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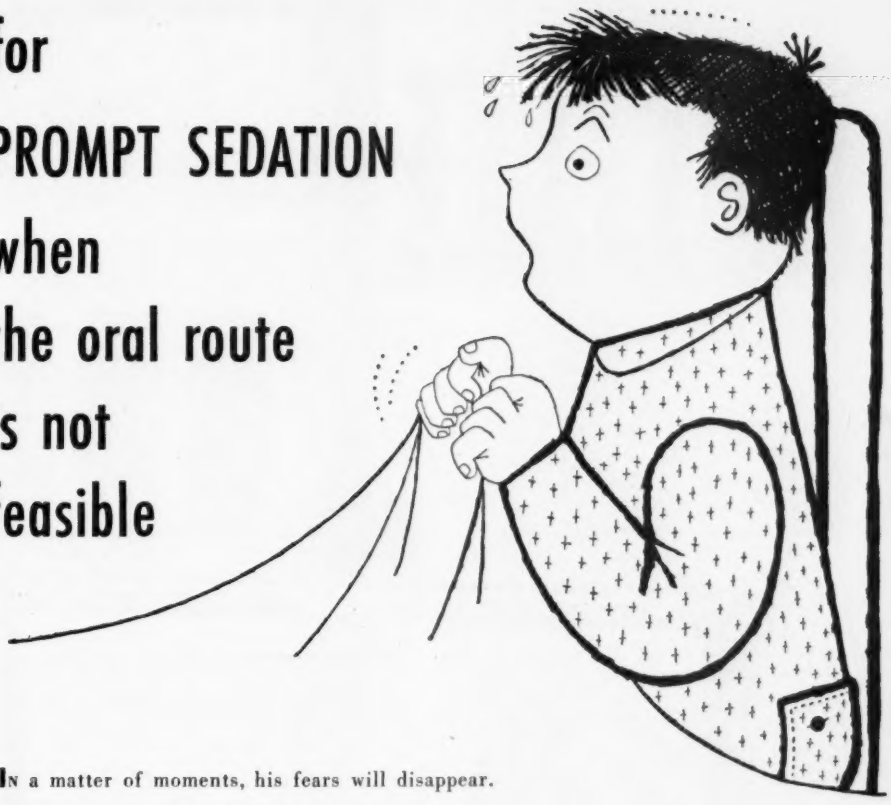

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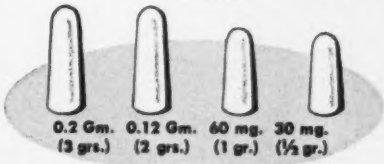

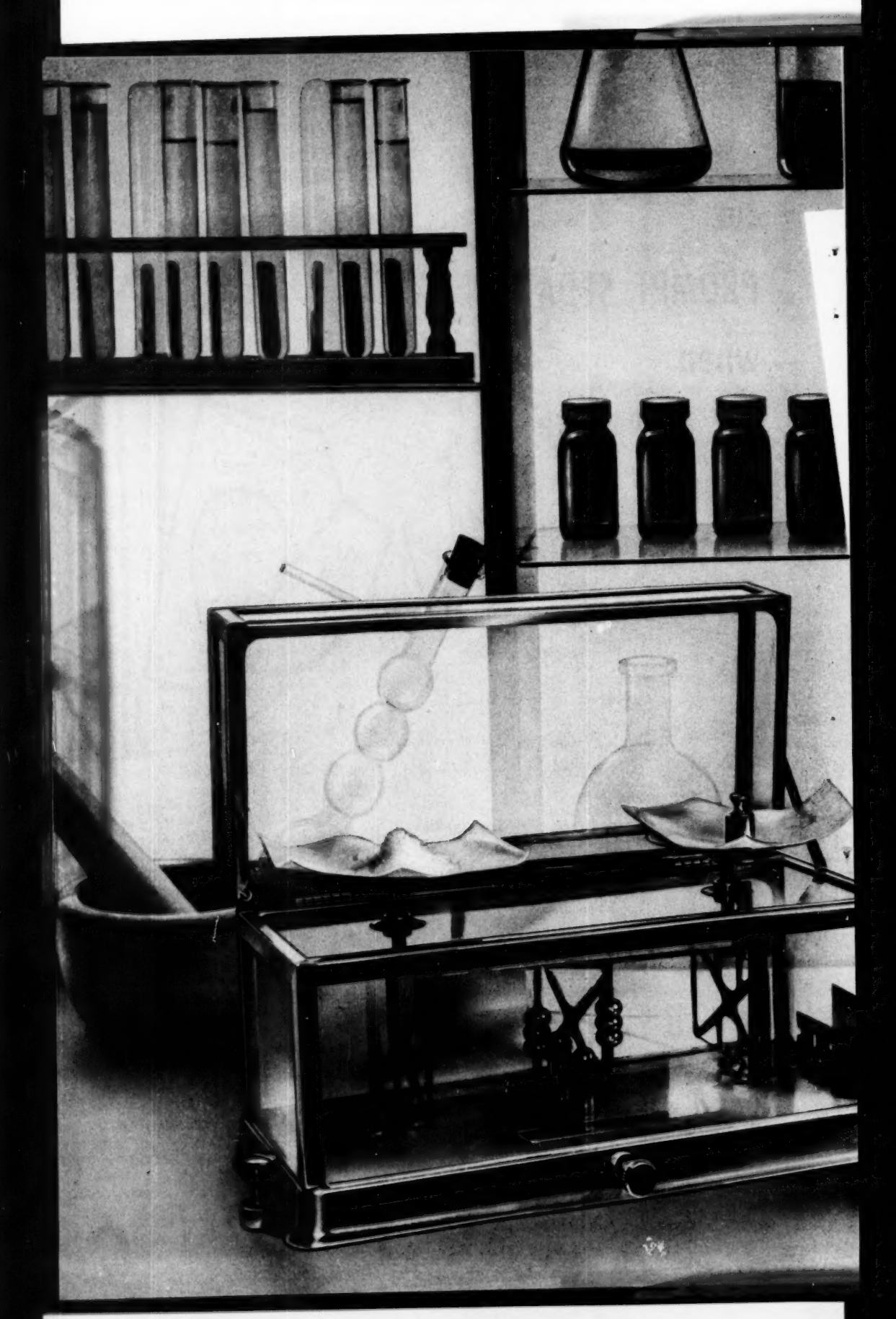

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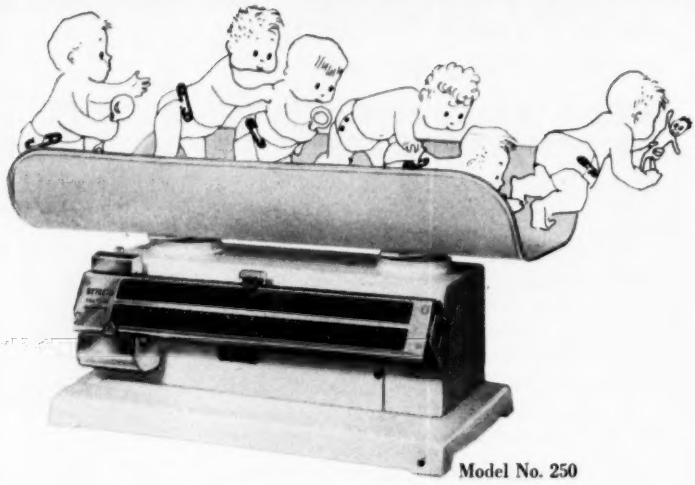

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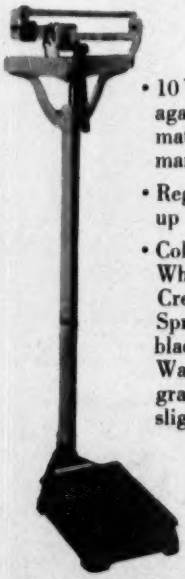

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2. Seidmon, E. E. P.: Am. J. Digest. Dis. *18*:274 (Sept.) 1951.
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American Journal of Diseases of Children

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MEASLES ENCEPHALITIS

A Follow-Up Study of Sixteen Patients

EDITH MEYER, Ph.D.
AND
RANDOLPH K. BYERS, M.D.
BOSTON

THE DISTURBED behavior of persons convalescent from acute encephalitides has been a subject of medical interest ever since the world-wide epidemic following the first world war. Opinion in regard to its genesis has gradually changed; whereas formerly the behavior complex, so well described, was felt to result from the action of the disease on the cerebrum, it is now more generally considered that the observed behavior is the result of the impact of environmental demands upon cerebral function qualitatively altered by disease. Whether the "postencephalitic behavior" following encephalitis lethargica is ever exactly duplicated in severity and duration after the common postinfectious encephalitides may be questioned; the fact that social maladjustments following the latter diseases are common cannot be doubted. The present study is an attempt to amplify and broaden the understanding of factors leading to behavior disturbances following attacks of measles encephalomyelitis treated at the Children's Hospital, Boston, between 1943 and 1949.

Though measles encephalitis has long been known, modern interest in it dates from the excellent monograph by Ford [1] published in 1928. Since then, many studies relative to etiology, clinical course, pathologic findings, and outcome, in relation to both survival and competence, have appeared. All reports agree that the survivors of an attack of measles encephalitis include a large percentage of noncompetitive persons, but there is no agreement concerning the basis for lack of competence. For example, Appelbaum and co-workers [2] stated that of 19 children discharged from the hospital as recovered 8 on subsequent follow-up showed various abnormalities, mostly in the behavior field. They went on to state:

> We are not, however, certain that the deviations in behavior are directly due to the encephalitis, for some of them could be explained perhaps equally well on the basis of parental attitudes, such as maternal overprotection after an illness, or other environmental influences.

Physiologic abnormalities of the cortex, as recorded on electroencephalograms, were studied by Jacobsson and Holmgren [3] in a series of 46 cases of measles encephalitis in the acute and convalescent stages. During the acute stage, high-voltage

This work was supported in part by a grant to the Children's Medical Center from the Hechscher Foundation.

From the Department of Pediatrics, Harvard Medical School; the Department of Social Relations, Harvard University, and the Children's Medical Center.

1. Ford, F. R.: Bull. Johns Hopkins Hosp. **43**:140 (Sept.) 1928.
2. Appelbaum, E.; Dolgopol, V. B., and Dolgin, J.: Am. J. Dis. Child. **77**:25 (Jan.) 1949.
3. Jacobsson, E., and Holmgren, B.: Ann. paediat. **173**:231, 1949.

slowing in all leads was the usual finding, but apparent clinical recovery preceded electrical recovery, and the latter did not always occur.

Hodes and Livingston [4] reported similar electroencephalographic tracings in acute measles encephalitis and reported that for seven patients, all of whom recovered clinically, the electroencephalograms became normal some time after apparent clinical recovery. Patients having acute measles without encephalitis showed normal tracings.

These clinical and electroencephalographic studies suggested that the usual methods of estimating recovery in cerebral disease have been inadequate. Crothers and Lord [5] observed in a group of children recovered from known encephalitis that abnormalities in mental functioning frequently occurred which were not evident in the usual quantitative appraisal of intelligence in terms of mental age or intelligence quotient (I. Q.). Similar findings were described in a paper by Byers and Lord [6] on children with known lead encephalitis. The first paper especially made the point that recovery to the *status quo ante* is not adequate in a child, though it is in an adult. Full recovery in a child implies resumption of orderly development leading to continuous new psychologic acquisitions and new adaptations.

The psychologic literature of the past 20 years contains many studies of the effects of cortical injury on cerebral function. Goldstein,[7] in his famous studies on adult patients, pointed to the impairment of the abstract attitude after brain injury. He also described what he called the catastrophic reaction or emotional panic which tended to occur when the organism was confronted with unexpected and repeated failure in relation to its own expectations or that of its environment.

In the children's field, Lord,[8] in her monograph "Children Handicapped with Cerebral Palsy," pointed out that the results obtained through standard intelligence scales were an unreliable index of learning ability after cerebral damage and that examinations of visuomotor functions and mental control were more relevant to the problem. Strauss and Werner [9] and Strauss and Lehtinen [10] found in various studies that brain-injured children showed impairment of mental processes in the areas of perceptual, perceptuomotor, and conceptual behavior. Characteristic difficulties described involved disabilities in relation to discrimination of main figure from background, spatial orientation in perceptions, and synthesis and generalization of ideas in thought processes. Meyer and Simmel [11] described similar distortions in mental functioning in an attempt to establish criteria for differential psychologic diagnosis in children with neurological disorders involving the cortex. In some types of injury perceptuomotor impairment seemed the most outstanding difficulty, whereas in others inability in learning and attention appeared to be more prominent. All observers agreed that a change in the quality of mental function

4. Hodes, H., and Livingston, S.: J. Pediat. **36**:577 (May) 1950.

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11. Meyer, A., and Simmel, M.: J. Abnorm. & Social Psychol. **42**:193 (April) 1947.

followed diffuse cerebral injury, rather than a reversion to patterns characteristic of younger ages, though age and developmental level at the time of the injury caused variations in the detail and form of the psychologic result. Descriptions of various emotional reactions, such as tension and anxiety in children with cerebral disease, particularly in relation to the growing demands of the environment, were common.

Furthermore, Bond and Appel,[12] in their monograph describing the activities of the Franklin School of the Pennsylvania Hospital, demonstrated that marked amelioration of the "bad behavior" of postencephalitic children could be obtained when concessions were made within the environment to the needs of this very difficult group. As frustration and anxiety lessened, vindictive and destructive behavior diminished, sleep reversal vanished, and life became tolerable.

In the present study an attempt was made to apply these ideas to the care, by parents at home, of children recovered from the acute phase of measles encephalitis. For success, it seemed important to seek the answers to five questions. First, what was the developmental progress of the children following the acute phase of the disease? Secondly, should the term postencephalitic behavior be used to describe the complex behavior disturbances heretofore attributed to the disease, or could they be defined in terms of more concrete psychologic deficits whose presence led to the maladaptation? Thirdly, what plan of management might tend to forestall the maladaptation? Fourthly, how might one describe in psychologic terms the various stages of the recovery process? Finally, what influence had age at onset on the psychologic changes and behavior patterns?

Sixteen children who recovered from measles encephalitis between 1943 and 1949 formed the basis of the study. Ten of the children were seen frequently for psychologic study and guidance based on the findings over periods varying from six years to 14 months. The remaining six children were seen less regularly: Two were seen for the first time three or four years after discharge from the hospital; two more, though seen several times in the first years after the attack, did not return for further examination for intervals of approximately three years each, and, finally, two were seen only during the first year or 18 months after the attack. Audiometer tests were done on 10 children, but since no abnormalities were found in the audiograms and since the facilities for such tests were no longer easily available, further studies were not made. Medical and electroencephalographic follow-up examinations were done as required. The major emphasis has, however, been on psychologic reexamination at regular intervals.

The age of the children at the time of the attack varied from 22 months to 10 years, as shown in Table 1, in which is also included a summary of the clinical course of the attack of measles. It will be noted that one child suffered from measles and vaccinia at the same time, and obviously either or both diseases could have been etiologically related to the encephalitis. To the purist, such a case might seem unsuitable for inclusion in the series, but since each individual diagnosis of measles encephalitis rests on an etiological assumption, the inclusion of this case seemed to us to serve as a reminder of the fact that in other cases undiscovered agents of the same sort might exist.

12. Bond, E., and Appel, K.: The Treatment of Behavior Disorders Following Encephalitis: An Experiment in Re-Education, New York, Commonwealth Fund, Division of Publications, 1931.

It is worth noting that in two instances doses of gamma globulin had been given: In one instance the dose was given on the sixth day after exposure to a sibling, with little modification of the measles; in the second instance, a very large dose given concomitantly with the appearance of Koplik's spots had little effect on the disease. In the first case, fever and prostration began six days after the globulin was given and a rash developed on the fourth day of fever; in the second instance the disease was also average in its course. It is obvious that gamma globulin so used is not an absolute preventive of the serious encephalomyelitis following measles.

Table 2 is an attempt to summarize the acute neurological stage of the disease and relate it to the final outcome. Since the symptomatology of measles encephalitis has been discussed very fully in the literature, no attempt at full review is made in this paper. In the table, modification of consciousness, disorientation, and convul-

TABLE 1.—*Summary of Clinical Course* *

1	2	3		4	5	6	7	8	9	10	11	
Case No.	Sex	Age Yr.	Age Mo.	Known Exposure to Measles	Fever	Cough	Koplik Spots Observed	Rash Appeared, Days After Onset of Fever	Gamma Globulin Given	Interval from Rash to Neurological Symptoms, Days	Age at Last Examination Yr.	Age at Last Examination Mo.
1	M	1	10	+	+	+	+	3	0	4	5	0
2	M	2	4	..	+	+	..	4	0	13	6	3
3	F	2	6	..	+	+	+	4	0	0	6	..
4	F	4	1	+	+	+	..	3	0	2	9	..
5 †	F	5	3	..	+	+	..	2	0	4	8	3
6	F	6	..	..	+	+	+	5	0	4	7	6
7	F	6	1	..	+	+	..	2	0	7	7	7
8	M	6	5	+	+	+	..	4	0	8	9	6
9	M	6	6	..	+	+	..	4	0	7	11	6
10	M	6	7	+	+	+	..	3	+	4	7	2
11	F	7	2	+	+	+	+	2	+	5	11	8
12	F	7	3	..	+	+	+	2	0	3	13	..
13	F	7	6	..	+	+	+	3	0	4	9	6
14	M	7	11	+	+	+	+	2	0	3	12	..
15	M	8	..	+	+	+	+	2	0	7	11	..
16	M	10	6	+	+	+	..	4	0	3	11	6

* Plus signs indicate presence of signs and use of gamma globulin.
† Primary vaccinia coincided with measles.

sions are considered as evidences of cortical involvement; tremor, cranial nerve paralyses, ocular motor disturbances, respiratory anomalies, dysphagia, and the like are related to the brain stem; sphincter disturbances, areflexia, hyperesthesia, and hypoesthesia are classified as evidence of myelitis. Amaurosis, present to a marked degree, was a surprising finding in four cases. All children had cortical symptoms or signs, and 10 of the 16 children had clear-cut evidence of myelitis. Any spinal fluid which showed more than 5 white blood cells and/or a total protein value of more than 35 mg. per 100 cc. in the presence of a qualitatively normal sugar level was considered characteristic.

The course of the acute disease was considered as short when the children were discharged from the hospital as actively functioning persons within a few days or weeks of onset. Protracted courses were marked by long periods of interference with consciousness, often measured in months, difficulty in reorganization of walking or speech, and the like, and were generally associated with discharge of the patient from the hospital in a state of greatly modified independence.

TABLE 2.—*Summary of Acute Neurological Stage Related to Final Outcome* *

1	2		3	4	5	6	7	8	9	10	11	12	13	14	
Case No.	Age Yr.	Age Mo.	Cortex	Brain Stem	Cord	Visual Loss	Spinal Fluid Characteristic	Course	Acute EEG	Final EEG	Environmental Tolerance for Special Needs	Outcome in Terms of Social Behavior	Psychologic Outcome	Follow-Up Period Yr.	Follow-Up Period Mo.
1	1	10	+	0	0	+	+	Protracted	Slow	2/sec. wave and spike	Bad	Bad	Damaged	3	2
2	2	4	+	+	+	0	+	Short	Normal?	Fast	Doubtful	Good	Excellent	4	..
3	2	6	+	+	+	+	+	Protracted	.....	Normal	Good	Good	Damaged	3	6
4	4	1	+	+	0	0	+	Protracted	.....	Normal	Uneven	Poor	Damaged	4	11
5	5	3	+	+	+	+	+	Protracted	.....	Normal	Good	Good	Damaged	3	..
6	6	..	+	+	+	0	+	Protracted	.....	.....	Bad	Bad	Damaged	1	6
7	6	1	+	0	+	+	+	Protracted	.....	Slow	Good	Good	Damaged	1	6
8	6	5	+	0	+	0	+	Short	Grossly slow	Rare spikes	Good	Good	Excellent	3	1
9	6	6	+	0	+	0	0	Short	.....	Normal	Good	Good	Excellent	5	..
10	6	7	+	0	0	0	+	Short	Slow	Normal	Good	Good	In doubt	..	7
11	7	2	+	0	+	0	+	Short	.....	Spikes	Good	Good	Fair	4	6
12	7	3	+	+	+	+	+	Protracted	.....	Normal	Good	Good	Excellent	5	9
13	7	6	+	+	0	0	0	Short	Slow	Normal	Good	Good	Excellent	2	5
14	7	11	+	+	+	0	+	Protracted	.....	Borderline	Good	Good	Fair	4	1
15	8	..	+	+	0	0	+	Protracted	.....	? Fast	Bad	Bad	Fair	3	..
16	10	6	+	0	0	0	+	Short	.....	.....	Poor	Good	Excellent	1	..

* Plus signs indicate presence of neurological involvement. See text for explanation.

The psychologic studies were carried out by both interview and test methods. In almost all instances psychologic study began with an intensive interview with the parents during the period of hospitalization or shortly thereafter. A detailed history was obtained of physical, mental, and emotional development at various ages, of personality traits, relationship to family and outsiders, school history, interests, and stresses and strains both temporary and permanent. This interview served the purpose of defining, as well as possible, a picture of the child and his past development and allowed speculation about expectations for the future. In addition, it served as a basis for gauging, through acquaintance with the parents, what might be expected of them in the way of understanding of and cooperation with a guidance program during convalescence.

After discharge of the child from the hospital, one or both parents and the child were seen at intervals of a month or two for the first six months, and thereafter at intervals of a year. When the situation was well established after several years, the intervals were lengthened to two years or more.

The test methods used in the examination of all the children were varied according to their needs in different stages of recovery. Soon after the illness, because of rapid fatigue, short examinations only were feasible, and these were directed toward establishing a baseline by appraising the level of competence reached before illness, current learning ability and attention spans, comprehension of new problems, quality of speech in relation to enunciation, use, and content, and ability in use of hands. Subsequently, as physical recovery progressed, the psychologic examinations were lengthened and intensified. The usual test scales were supplemented by a series of specialized techniques, usually scored to percentile norms. This combination of methods, forming a flexible qualitative type of examination, had been found most useful in defining the defects resulting from damage to a previously effective brain. It has been described in detail in other publications.[13] The following tests were used:

1. Test Scales

   Gesell Developmental Schedule
   Revised Stanford-Binet Intelligence Scale
   Wechsler Intelligence Scale for Children (W. I. S. C.)
   Wechsler-Bellevue Intelligence Scale (W. B. I.)

2. Learning and Attention Tests

   Rey: Nonverbal Learning Test
   Learning of Word Series
   Learning of Picture Series
   Memory for Pictures (adapted from Minnesota Pre-School Scales)

3. Formboard Tests

   Gesell Three Figure Formboard
   Wallin Peg Boards (with adaptations by E. Lord)
   Seguin Formboard
   Five Figure Formboard (Pintner-Patterson Series)
   Casuist Formboard (Pintner-Patterson Series)

4. Block Design Test

   Kohs Scales
   Goldstein-Scherer Scales (modified for children)

13. Byers, and Lord.[6] Meyer and Simmel.[11]

5. Drawing and Design Tests

Goodenough: "Draw a Man"
Rey: "Lady Walking in the Rain"

(*a*) Copy of Design

Gesell Geometric Forms
Bender Visuo-Motor Gestalt Test
Rey-Osterrieth: Complex Figure

(*b*) Memory for Design

Gesell (modified)
Ellis Visual Design Test
Benton Visual Retention Test

(*c*) Goldstein Stick Tests

Copy and Memory (modified for children)

6. Other Nonverbal Tests

Wood Picture Completion Test
Porteus Maze Test

7. Verbal Automatisms

Counting, days of week, months of year, arithmetic facts, etc.

For no one child were all these tests used, but selection was made in relation to age and circumstances of the examinations.

Psychologic tests were directed toward detection of deviations from the normal that might explain the difficulties in mental functioning not adequately revealed by the usual globally scored examinations. Since such difficulties were not reversions to younger mental levels but represented perversions, they were not scorable in terms of mental age or I. Q. but could be described only qualitatively or on a percentile basis. In the light of present knowledge of psychologic function in structural disease of the brain, it seemed certain that abnormalities definable by these tests were based on structural disease rather than on functional personal dynamics. The tests chosen seemed, in the children's field, the most suitable for the purpose. Projective techniques were used occasionally but were not made part of the regular examinations.

In Table 2, a general statement of the results of the final psychologic examination of each patient has been attempted in one word in Column 13. Column 12 indicates the estimate of parents, schools, camps, and other social agencies of the behavior of the child in social terms. Column 11 indicates our estimate of the ability of the parents, schools, and other agencies to make adequate adjustments to the needs of the children as exemplified by the psychologic findings. Columns 9 and 10 relate to electroencephalographic findings in the acute stage and at the end of the follow-up period.

Neurological examinations at the time of final follow-up showed astonishingly few abnormalities. Most of the children with protracted courses in the acute stage showed some signs of neurological nature for months or a few years after discharge. The functional evidence of myelitis was usually slow to clear, and 2 of the 10 children who had clinical evidence of myelitis in the acute stage still showed poor sphincter control one and one-half and six years, respectively, after the attack. Return of motor function in the legs occurred in all the children, usually in a matter of months, but often required years to reach its maximum. Normal vision was

present in all the children at follow-up, and in all those who became blind during the illness vision began to return within a few weeks after onset. No abnormalities of hearing were found in the 10 children examined at follow-up. Except for one child who showed wave and spike complexes on follow-up, final electroencephalographic findings might be mildly aberrant in spite of excellent psychologic and social recovery, and normal tracings were often seen in the presence of persistent psychologic impairment.

As shown by the table, there was a close correlation betwen the length of the acute course and the psychologic outcome. All the children who had short acute courses in the hospital, regardless of age (namely, Cases 2, 8, 9, 11, 13, and 16), had a fair to excellent restitution of psychologic function. Only one child (Case 10), whose final examination followed his illness by seven months, still showed important psychologic damage, and he was improving.[14]

The evolution of psychologic recovery in the group with short acute courses was interesting. Although all appeared clinically recovered on discharge from the hospital or soon after, some could not function efficiently for as long as a year after discharge. Careful psychologic study during the period of recovery demonstrated disabilities which would not be revealed in global scores or I. Q.'s. They were detectable, however, by special test procedures. When they went home all of the children of this group had normal I. Q.'s, adequate reasoning ability, and essentially unimpaired comprehension of form materials (formboards, block designs, and copy of forms). Attention and memory for new materials were, however, usually impaired as measured by memory for designs, pictures, and words. Their learning ability was often noticeably diminished by their lack of staying power and difficulty in completing a prolonged task. Unsteadiness and clumsiness of the hands seemed to interfere with competence in a few. One preschool child, previously very self-sufficient, went about the house stamping her foot and crying at her mother, "I hate you; I hate you." When her difficulty in manipulating buttons, spoons, and the like was called to the mother's attention and she was asked to help the child in dressing, eating, and other tasks, the overt antagonism disappeared promptly.

Reexamination one to four years after illness by the Wechsler Intelligence Scale for Children showed for five of the six children better scores in nonverbal than in verbal parts of the scale. Performance was adequate or better in relation to form comprehension (block designs and object assembly), but slight difficulties in verbal expression or elaboration of ideas were present in three children. Such tendencies were not striking enough, however, to show up as significant numerical deviations in the test scores.

Much more obvious disabilities were observed in the nine children who were discharged from the hospital after prolonged acute illnesses. In all walking was modified or absent for five weeks to seven months. On leaving the hospital, one was blind, one was aphasic, and two had marked interference with word recall. Emotionally the children showed a variety of reactions: Four were noted to be very quiet and slow in their responses; two were described as very labile in their moods, with a pattern of crying and resistance appearing overeasily, and one, after recovering his motor function to a great degree in the hospital, showed uncon-

14. Since completion of this manuscript, this child (Case 10) has been reexamined and improvement has continued; he seems well on the way to restitution of his status before illness.

trollably aggressive behavior. Four were noted to be mainly impulsive and excitable, and their thinking processes were characterized by flight of ideas.

To the casual observer in the ward, seven of these children appeared alert and "probably back to normal." For instance, a note on the record of one child (Case 15), written by a very intelligent physician, stated: "A. is wonderful; he walks and talks." Compared with his condition a week or two before, when gavage feeding was necessary, the child's progress was wonderful, but overenthusiastic insistence on this boy's recovery may well have been one of many factors that led to his exclusion from school three years later.

Psychologic examination of seven of these nine children at the time of discharge from the hospital showed that only one had recovered her previous adaptability, though she was still very excitable. The other six were confused, flighty, and unable to give attention in the test situation long enough to solve problems requiring sustained thinking. They were in general able to reactivate previously learned material and thinking patterns in short bursts of effort. Two of the children who had recently learned how to write and print now remembered printing only. One boy who had previously shown a reading difficulty was unable to recognize words he had known reliably in school prior to his illness.

After their discharge from the hospital, the children's psychologic difficulties seemed largely dominated by difficulties of attention. Many of the special aberrations, such as inability to distinguish between details and the whole, confusion of background and main figure, and loss of learning ability, seemed for the most part related to loss of mental control.

An attention difficulty in the verbal field was exemplified by a boy of 8½ years, who five months after discharge from the hospital was asked by the psychologist, "What would you do if, on the way to school, you found you were in danger of being late?" "I'd climb trees and go behind houses," he replied. "Why would you do that?" she asked. "Well, if I was in danger . . .," was his reply.

It is obvious that the child's attention was unable to encompass a rather long question, but that he did react to the detail word "danger," in relation to which he made an impulsive decision. It is easy to see how such defective thought processes would lead to behavior quite incomprehensible to children and adults and would certainly arouse ridicule and teasing, if not disapproval, correction, and punishment. When such an attention defect persisted, as in Cases 4 and 5, it interfered with new learning and mental development.

Defects in perceptual-spatial organization were exhibited by seven patients in the production of complex designs, letters, and mosaic patterns with blocks (the so-called block designs) by copy or from memory. Such symptoms have been frequently and adequately described in relation to cerebral injury. As an example of such distortions in the perceptuomotor field, Figure 1 will suffice. It was apparent that the patient (a 10-year-old boy) perceived the model figure in an unusual way: Instead of two squares, one within the other at an angle, he saw and reproduced only one square with isolated triangles attached to its corners. He was unable to appreciate the whole figure in its proper relationships, since his attention was centered on only one detail of the figure at one time.

It must be noted here that the persistence of such defects in children who had not been previously schooled made the acquisition of the primary school techniques (writing, reading, and especially arithmetic) very difficult, if not impossible.

This is not the place to discuss in detail the significance and the genesis of perceptuomotor distortions. Our findings seemed to indicate that they might well have arisen secondarily to attention defects and lack of mental control, which if continuous and persistent might create faulty perceptual habit patterns and disturb smooth mental development. Such an interpretation would find points of agreement with various modern theories of perceptual activity.[15]

In the children with the severe disease in whom it was possible to obtain an I. Q. at all soon after illness, the quotient was adequate, though restlessness and fatigability were prominent. In subsequent quantitative tests, all the children with a short course and five of those with a protracted course gave adequate results. Disabilities of functioning, sometimes persistent in some degree, were so mild as to be manageable through substitution or had completely disappeared.

Five of the nine children with the severe disease showed deterioration in I. Q.'s through the years, though it was sometimes three years or more before the I. Q. adequately described the mental difficulties. Such a drop in I. Q. was a result of increase in the child's chronological age, unaccompanied with a parallel advance in

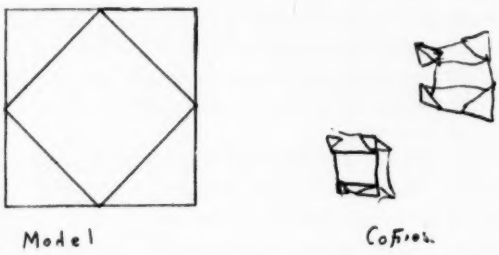

Fig. 1.—Copies made from model by a 10-year-old boy with defects in perceptuospatial organization.

mental age owing to attention defects and mental disorganization. These subjects were no longer able to get along with previously learned intellectual patterns and automatisms. The problems now facing them required the acquisition of new learning and intellectual syntheses which was impossible for them. Though the individual test scores in learning tasks often improved over the years, the general level of intellectual efficiency dropped, as evidenced by the I. Q. This course of events is shown for Cases 4 and 5 in Figure 2.

Among the severely affected, the age at onset seemed to color the result. The older children (especially Case 14) seemed to have developed better, in spite of demonstrable and persistent perceptual defects, than younger children even less affected. This difference was independent of the severity of the illness and seemed to be the result of the greater experience and wealth of previously acquired working patterns in the older children. With the help of such a background, the older children seemed able to build new intellectual organizations even with impaired perceptual processes, whereas the younger ones had to attempt the acquisition of the more

15. Piaget, J.: Psychology of Intelligence, London, George Routledge & Kegan Paul, Ltd., 1950. Werner, H.: Comparative Psychology of Mental Development, Chicago, Follet Publishing Company, 1948.

elementary adaptations with defective tools. Similar observations have been recorded by Hebb.[16]

The personality changes and behavior disorders were rather clearly related to the observed psychologic disabilities described above; for the relation of the individuals to their environment, as shown in social response and emotional reactions, was distorted by the difficulties of attention, perception, and learning. The patients impulsively reacted to immediate stimuli, details acquired disproportionate importance in their decisions, and the relation of object and background became confused. As a result, the patient found himself too frequently and unexpectedly frustrated, blamed, and unsuccessful in the eyes of his family, school, or community. Reactions similar to Goldstein's catastrophic reaction expressed themselves as tantrums, mood swings, and aggressiveness. When such traits were already inherent in the personalities of the patients, they tended, as in Case 15, to be reenforced by the

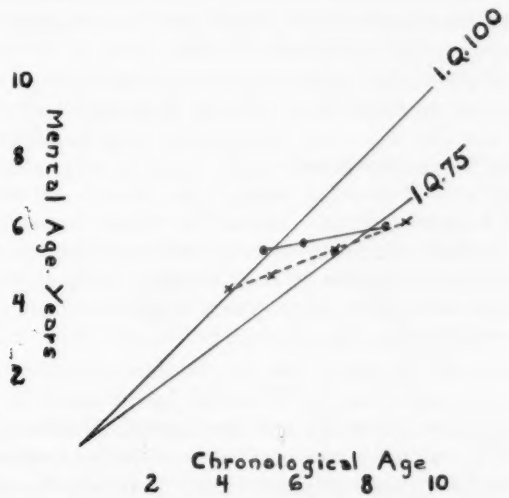

Fig. 2.—Development of gross mental defect owing to persistence of attention, perceptual, and learning defects produced by measles encephalomyelitis in Case 4 (x--x) and Case 5 (o--o). In both instances the first I. Q. values were obtained two to three months after onset of disease.

environmental stresses, while in other children timidity, repression, and anxiety resulted.

Environmental flexibility, such as tolerance and understanding by parents, and willingness of schools to repeat previously learned material rather than insist on new accomplishment and to modify disciplinary standards, had a clear bearing on behavior. In the children with short acute courses, it was usually possible to persuade parents and teachers to "hold the fort" pending recovery, and, though some difficulties arose, they were relatively short-lived, since the parents could for themselves observe improvement and could, therefore, understand the philosophy of waiting out the convalescence.

In the more severely damaged children, the modification of the environment was more difficult and was usually impossible when dealing with unintelligent or emo-

16. Hebb, D. O.: Organization of Behavior: A Neuropsychological Theory, New York, John Wiley & Sons, Inc., 1949.

tionally disturbed parents. In some instances, wise and patient parents were able to protect their children throughout a long convalescence and help them to achieve an apparently satisfactory social adjustment, in spite of a considerable remnant of psychologic damage. In Case 14, such a result seemed to be related to the attitude of parents and schools, as well as the rather advanced age at onset. In Case 15, on the other hand, a more perfect psychologic recovery could not be utilized by the patient, possibly owing to the year of frustration imposed upon a previously rather aggressive personality by an unsympathetic mother and a school system which insisted on conformity and promotion. Even without the handicap of encephalitis, it is to be noted that he lived in a disorderly household in a rather poor community.

In some of the younger children, flightiness and instability appeared to the parents by no means distressing. The resultant liveliness and volubility were often welcomed by them as an evidence of recovery and were often encouraged. These children unhesitatingly established their contact with life on that basis and continued to be carefree, overactive, and uninhibited up to the time at least that academic failure and social pressure brought overt conflict into their lives.

Some of the older children, however, were more aware of their own confusion and unreliability. In particular, those who had previously been orderly and considered in their activities were much distressed by their inabilities and even occasionally expressed themselves to this effect. Some of these children tried to be especially careful and, in so doing, became overcautious and restricted in their attitudes and hesitant in expressing themselves. Those, on the other hand, who had been lively, restless, and impulsive prior to illness came in conflict with their environment through exaggeration of these qualities. In short, it seemed that the personality changes never arose as completely radical ones but appeared as overemphasis of personality traits already present.

In any event it did not appear that environmental adjustments basically influenced the pathology underlying the intellectual deficits caused by the disease. In Case 5, for example, in spite of the fact that cheerful, affectionate, and intelligent parents were able to maintain a seriously impaired child on an emotionally quiet and comfortable basis for a period of years, her I. Q. fell steadily into the range of clear-cut mental inadequacy as a result of her defective attention and perception.

COMMENT

Measles encephalitis, presumably in common with other acute reversible encephalopathies, when it occurs in children presents problems which have not been well defined or recognized. Recovery to the previously achieved level of competence is seen in a large proportion of cases in a matter of weeks or months, and may mistakenly be considered complete. Complete recovery in childhood implies the ability to acquire new knowledge and new adaptations, and, unless this capacity is fully restored, frustration and disappointment are likely to overbalance satisfactions in school, home, and social contacts.

Psychologic study of a group of children convalescent from measles encephalitis, herewith reported, shows that after apparent recovery, abnormalities of mental functioning can be demonstrated in a very high proportion after neurological and electroencephalographic evidences of the disease have cleared. Easy fatigability of intellectual function, defects in attention, defects in perceptual-spatial organization,

and defects in learning capacity tend to persist for months, or even permanently, in about a third of the children. Patients with short acute courses fare better in this regard than those with prolonged courses. When the psychologic defects persist, inability to acquire new knowledge and adaptations produces a relative intellectual deterioration over the years. Motor disabilities may add to the patient's difficulties, but they appear to be temporary as judged from our material.

The child's inability to live up to the expectations of home, school, and society produces emotional stress expressed as either retreat into himself or aggressive rebellion.

A plan of life which makes the necessary concessions to his disability and allows the child emotional ease during the period of waiting out the recovery process may make the eventual resumption of his responsibilties easier. In preschool children modifications of the mother's expectations in regard to dressing, eating, toilet habits, and the like, need to be combined with direct emotional support, affection, and patience. Schoolchildren usually do better with a home teacher for months or even a year or more after an attack, or, if this is not possible, repetition of previous school grades on a modified schedule may work out. If it is evident that the child can carry his expected load after experimenting with smaller loads, he should be allowed to do so but with some reluctance.

Age at the time of the attack influences the outcome. Older children, because of their more elaborate foundation of learning, are more likely to remain competitive, in spite of incomplete intellectual recovery, than are younger children who must then acquire even the most fundamental learning with defective tools.

Although it seems that a program based on concession to observable psychopathology often may diminish anxiety and tension and tend to improve behavior, there is no evidence that the fundamental cerebral pathology can be influenced thereby.

SUMMARY

The clinical course and development following measles encephalitis, as seen in patients at the Children's Hospital, Boston, between 1943 and 1949, are reviewed. The psychologic and neurological disturbances following this disease are discussed, and their significance is outlined.

REPORT OF CASES

CASE 1.—The family history of a boy $1\frac{10}{12}$ year of age (C. M. C. 317742) was not remarkable.

Personal History.—The pregnancy was normal, with a normal primiparous delivery. His birth weight was 8½ lb. (3,856 gm.). There was no neonatal difficulty, no reaction to prophylaxis, and no illness prior to present illness. The patient walked alone at 13 months of age and spoke words at 15 months and simple combinations of words at the time of illness.

Present Illness.—The child had had definite exposure to measles two weeks prior to his admission to the hospital. Seven days before admission he had a cough and Koplik spots. Five days before admission rash appeared. Four days before admission penicillin was given, with improvement in his condition. Penicillin was also given three days before admission. One day before admission he was drowsy and irritable and would not stand. On the day of admission he had a right-sided convulsion followed by coma.

Physical Examination.—On admission to the hospital his temperature was 102 F., pulse rate 110, and respiration rate 34. He showed a fading maculopapular rash. He was unconscious and mildly cyanotic and had intermittent twitching of his right arm and leg. He responded to painful stimuli by weak movements of his left arm and leg but did not move the right extremity

voluntarily. His lungs showed diffuse moist rales, and his eardrum membranes were injected. His spinal fluid contained 10 lymphocytes, and the total protein value was 41 mg. per 100 cc. His white blood cell count was 38,000, with 80% polymorphonuclear cells.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—The child remained semicomatose for two days, with one generalized convulsion 24 hours after admission. He then began to be more aware of his surroundings over the next several days, with variable tendon reflexes but a constant Babinski sign on the right. By the fifth day he was actively sitting up, drinking, and eating well when fed but was totally blind, though his pupils reacted briskly to light. By the 7th day he could perceive bright objects, but when he was taken home on the 22d day he still saw very little. He was still not talking and was extremely anxious and fearful. In the last few days in the hospital he used a few phrases like "pretty doll" appropriately. Roentgen examination of his skull, sinuses, mastoids, and chest showed no abnormalities on the day after admission. An electroencephalogram revealed random two- to three-per second activity in all leads (Fig. 3, upper).

At home, he was difficult, irritable, and overactive.

Three years later, at the age of 5 years, he was returned on request to the hospital by his aunt, who said his mother was totally unable to manage him. She described him as impulsive, stubborn, and unable to get along with other children. He was the terror of the neighborhood. On examination his fundi, pupils, and extraocular movements were all normal. He saw small objects, such as pins, and picked them up quickly. His hearing of speech was adequate. His speech was immature, but with good pronunciation. His attitude and emotional responses were extremely negativistic. A neurological examination revealed nothing remarkable. His gait was well organized.

Psychologic examination showed a child with very short attention spans and very poor learning ability. He had marked difficulty in drawing simple designs, being unable to orient the pencil stroke correctly. While most of his nonverbal performances were at best on a 3-year level, his verbal ability was on a 4½ to 5-year level in situations which did not require a prolonged reasoning process. He was seldom calm enough to work at his best capacity. It seemed certain that his difficulties in attention and perceptuomotor areas would hinder his progress in school to a greater degree than was indicated by his I. Q. of 88. An electroencephalogram at this time showed a background rhythm of six to eight per second in all leads, with frequent two-per-second spike and wave complexes of greater voltage and frequency in the left frontal and precentral leads (Fig. 3, lower).

Summary.—An infant of 22 months acquired an encephalopathy five days after his measles rash; the encephalitis ran a protracted course of right-sided convulsions, coma, and blindness. Anxiety, confusion, and marked electroencephalographic slowing remained prominent when his mother took him home on the 22d day. At this time he could sit, stand, and use a few words. His mother could not make the adjustment required to meet his short attention span, impulsiveness, and confusion, and he became unmanageable. At 5 years of age he was negativistic and immature emotionally, his vision was good, but psychologic examination still showed short attention spans, distractibility, and perceptuomotor disorientation which will almost certainly prevent his attaining the behavorial level expected with a low average I. Q. His electroencephalogram was still grossly abnormal, suggesting the probability of future convulsions.

CASE 2.—The father, mother, and one older sibling, a boy 2 11/12 years of age (C. M. C. 307608), were just recovering from measles.

Personal History.—The pregnancy, delivery, and neonatal period were unremarkable. The patient was always very small and had a small appetite. He never had any convulsions, severe illness, or pica. No prophylaxis had been given. He maintained sitting posture at 6 months of age, walked at 14 months, and used a number of single words at the time of admission to the hospital.

Present Illness.—Twenty-one days before admission the patient had coryza, fever, and vomiting. Eighteen days before admission a rash appeared in the mouth and on the skin. The diagnosis of measles was made. Because he was weak, he was put to bed until 11 days before admission; he was then allowed up, but he was weak and unsteady with marked tremor, though he felt well. Seven days before admission a diagnosis of sore throat was made, and

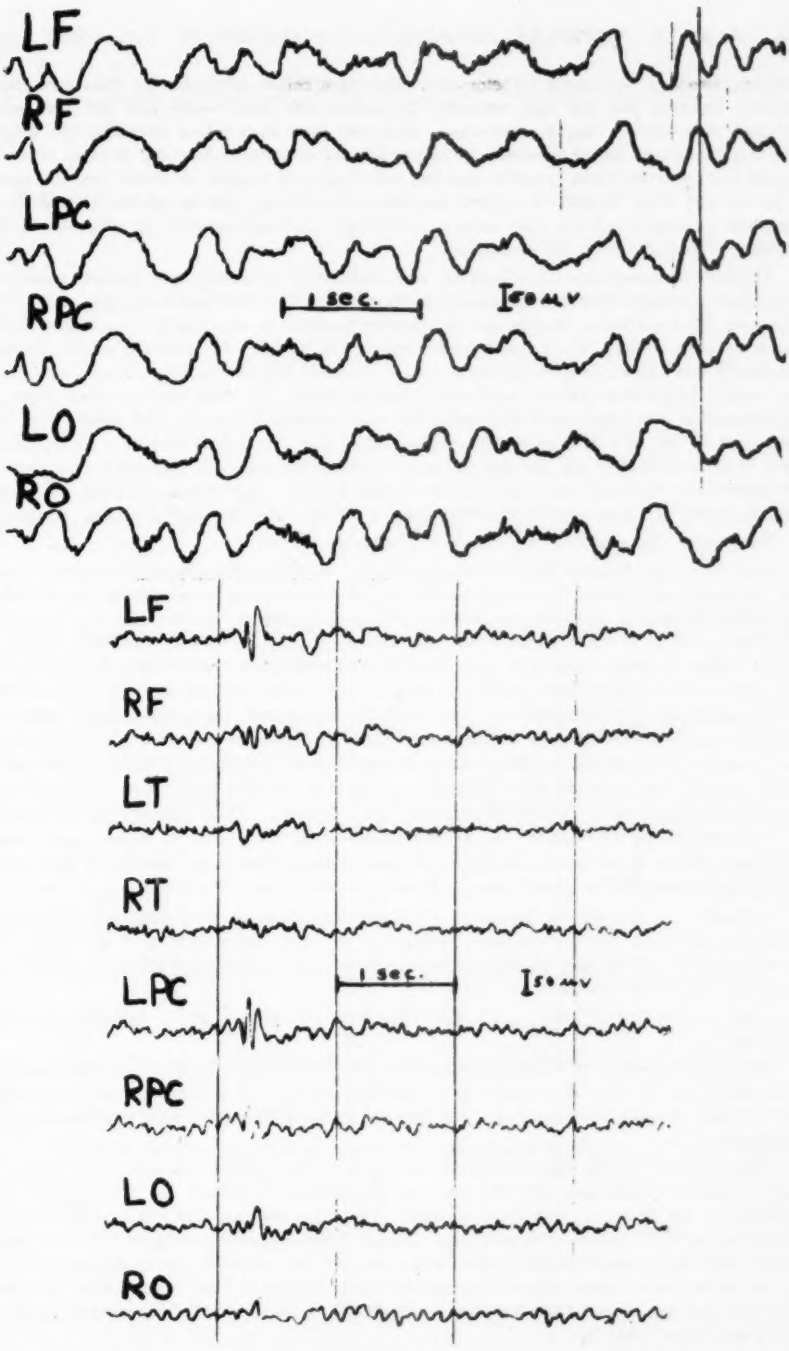

Fig. 3 (Case 1).—Upper, electroencephalogram made at age of 22 months, during acute attack of measles encephalitis, showing diffuse slowing. Lower, electroencephalogram made at age of 5 years, three years after acute attack, showing spike-wave complexes in left frontal and left precentral leads.

sulfonamide drugs were given for two days. Five days before admission the child was much weaker; his neck was stiff and retracted; the tremor was much worse, and the jaws were clenched. He was not clearly unconscious. Four and three days before admission the tremor was less. Two days before admission he had recurrence of tremor, clenching of jaws, constant crying, and apparent fright. Lumbar puncture was done at a hospital in Maine, and the spinal fluid was said to be normal. A calcium preparation was given, with no effect. Because these symptoms continued and the child became increasingly confused mentally, he was sent to the Children's Medical Center for evaluation.

Physical Examination.—Consciousness was moderately impaired; the patient sometimes responded to simple requests. He seemed hyperesthetic. The neck and back were stiff. The eyes were not remarkable; funduscopic examination revealed no abnormality. No cranial nerve paralyses were present. There was severe tremor of all muscles on voluntary effort. Passive movement was difficult because of resistance and apparent pain on handling. Active movement was weak. The tendon reflexes were generally hyperactive, but there were no clear signs of involvement of the spinal tract. The sphincters were essentially normal. The white blood cell count was 10,200, with 55% polymorphonuclear cells. The spinal fluid showed a normal sugar level, total protein of 14 mg. per 100 cc., and 5 lymphocytes per cubic millimeter. An electroencephalogram disclosed four- to five-per-second activity, with many scattered three-per-second waves, and was considered as probably somewhat slow for his age (Fig. 4, upper).

Diagnosis.—The diagnosis was measles encephalitis.

Course.—In the hospital the child showed marked confusion and intention tremors, though he was never unconscious. In a week his tremor had subsided, and on psychologic examination he seemed lacking in strength, but otherwise was not abnormal. On the 12th day, when he was discharged to the care of his mother, he walked steadily and talked reasonably.

On follow-up examination four years later he was cooperative and pleasant, but rather shy and apprehensive. His mother seemed to supervise him rather too rigidly. He weighed only 32 lb. (14.6 kg.) at 6 3/12 years of age. Results of physical examination were otherwise unremarkable. On the Wechsler Intelligence Scale for Children he had an I. Q. of 100 on the total scale, an I. Q. of 105 to 110 on the performance scale, and an I. Q. of 95 on the verbal scale. Special tests revealed slight difficulties in learning and attention, which may well have been in consonance with his early development. He was doing well in kindergarten and was to be promoted to the first grade. An electroencephalogram showed 5- to 7-per-second waves with much 22- to 25-per-second activity in all leads, a record which was considered abnormally fast (Fig. 4, lower).

Summary.—A 2½-year-old boy acquired measles and two weeks later displayed neurological symptoms, including tremor, confusion, stiffness of the neck, and clenching of the jaws. The spinal fluid showed minimal changes. Recovery from acute symptoms was rapid and in four years was apparently complete.

Case 3.—The family history of a girl 2 9/12 years of age (C. M. C. 304136) was noncontributory.

Personal History.—The personal history was noncontributory. Development was average: The patient sat at 7 months, walked at 14 months, talked at 15 months, and was completely toilet-trained at about 2 years of age. She had had otitis media treated with sulfonamide drugs repeatedly.

Present Illness.—Four days before her admission to the hospital the patient had fever, an upper respiratory infection, and red eardrum membranes, for which she was treated with sulfadiazine for 48 hours, with good response. Two days and one day before admission, the symptoms recurred and a frequent, dry, hacking cough became prominent. Twelve hours before admission a maculopapular rash appeared on her face and neck and spread to the trunk. A few hours before admission she became drowsy and listless. Two hours before admission she had three generalized tonic and clonic convulsions, during one of which she fell against a stove and burned herself.

Physical Examination.—Physical examination showed a well-developed, acute measles rash on the skin and Koplik's spots on the buccal mucosa. Many rhonchi were present in the lungs. The eardrum membranes were bright red. A purulent nasal discharge was present. The tendon

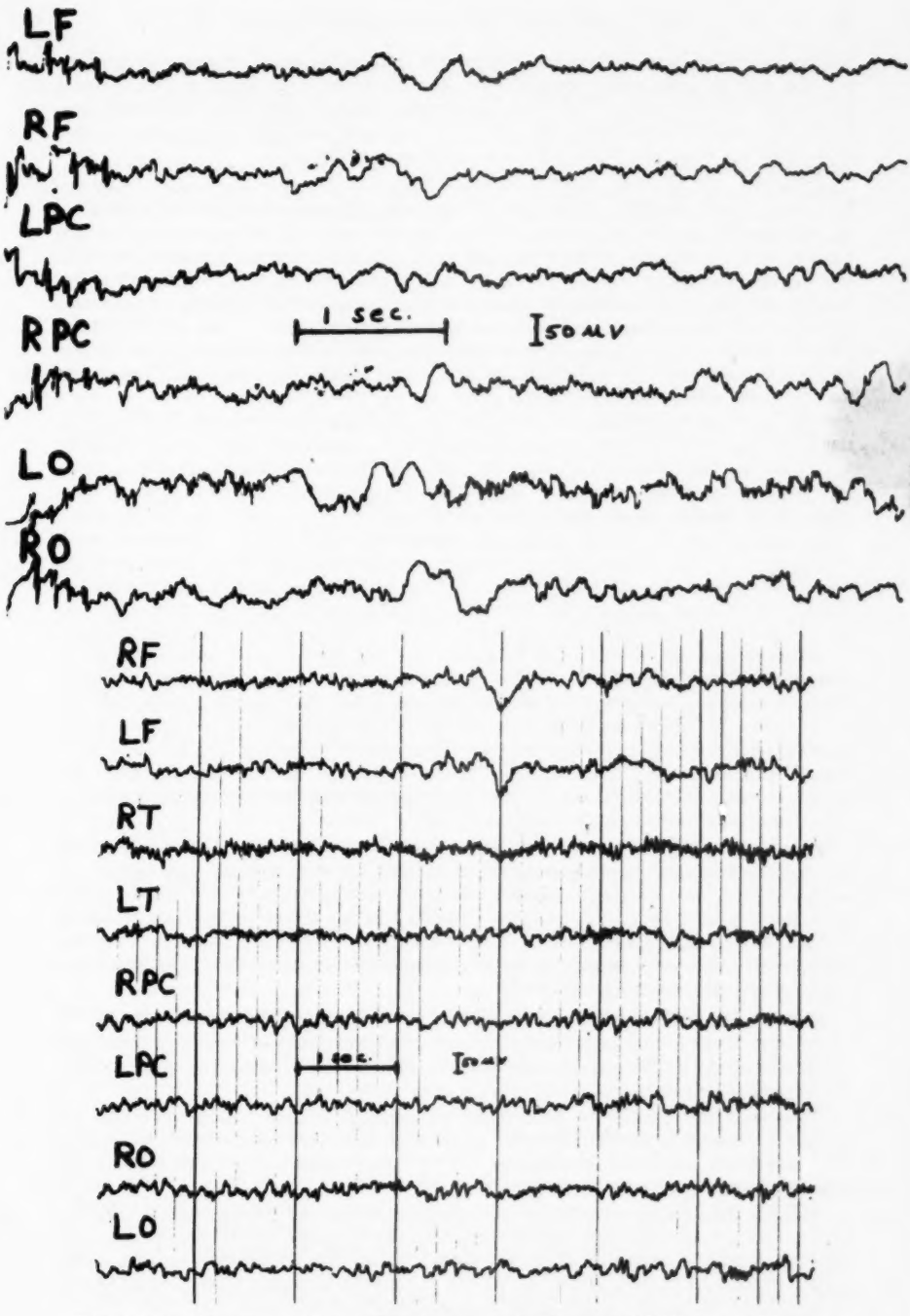

Fig. 4 (Case 2).—Upper, electroencephalogram made at age of 2-4/12 years, during acute attack, showing borderline slowing. Lower, follow-up electroencephalogram made four years after illness, showing fast activity.

reflexes were hyperactive, and Babinski reflexes were present bilaterally. She was unresponsive and stiff, with the jaws tightly clenched. Her lips and tongue were bitten, and there was a burn on the dorsum of the left hand. The spinal fluid showed 21 white cells, of which 18 were lymphocytes and 3 polymorphonuclear cells, and a total protein of 15.6 mg. per 100 cc. Her white blood cell count was 17,100, with 91% polymorphonuclear cells.

Diagnosis.—The diagnosis was measles encephalitis.

Course.—Roentgenograms of her chest showed mild diffuse peribronchial infiltration, but no consolidation. In spite of sedation, her convulsions recurred for 24 hours, and after that recovery was slow. For more than a week she was unable to sit up in bed because of weakness and dizziness and had to be propped up in bed and tube-fed until the eighth or ninth day. By the 10th day she could maintain her sitting balance for two or three minutes. At this time she had a definite hemiplegia, with increased tendon reflexes in the left arm and leg, and a Babinski sign on the left. She seemed completely unaware of her surroundings, and it was not clear that she saw, but she did turn her head toward sounds. On the 11th day her mother took her home with the full realization that she was not yet recovered.

Nine weeks after discharge, voluntary use was returning to the left hand; she did not stand; she understood language and would look at objects on request, though she did not speak.

Six months after admission she was walking, and nine months after onset she began to use single words, could get on and off chairs, and resume her previous excellent toilet habits during the day, though she still was wet at night.

At 3 7/12 years of age she was talking in single words and a few word combinations. In psychologic tests her comprehension of situations was predominantly on a 3-year level.

At 4 7/12 years of age she was somewhat babyish in her speech and deportment, but her general test level was about 4 years, with poorer performance in relation to abstractions. As the youngest of a large family, she was easily babied and protected in a good-natured way.

At 6 years of age the child was in kindergarten and liked it. Her speech was poorly articulated, her face expressionless, and her gait rather stiff, with loss of associated movements. Visual and auditory acuity was satisfactory. She had rather lively tendon reflexes, more so on the right. Psychologic examination showed an I. Q. of about 85. She had short attention spans, was distractible, and showed many signs of confusion in the perceptual field. Emotionally she was immature and egocentric. Enuresis was still a problem. An electroencephalogram was normal. It was felt that she should repeat kindergarten, since her poor spatial orientation did not qualify her for first-grade work.

Summary.—A 2 8/12-year-old child acquired measles, with drowsiness, convulsions, coma, and spinal fluid changes appearing on the day of the rash. Recovery from the acute episode was slow, and at 6 years of age she seemed impaired in comparison with the promise of her development prior to the illness. The type of psychologic impairment encountered was rather characteristic of that produced by a diffuse cortical injury. No striking behavior aberration had appeared, apparently because of the almost automatic protection from intellectual and emotional pressure provided by her family.

CASE 4.—The family history of a girl 4 1/12 years of age (C. M. C. 293955) was unremarkable.

Personal History.—According to the mother, the patient talked at 9 months of age and walked at 18 months. She entered kindergarten at 3 9/12 years and had learned to make letters and to count meaningfully.

Present Illness.—Twenty-one days before her admission to the hospital the child was exposed to measles in school. Five days before admission coryza and cough were present. Two days before admission rash appeared. On the day of admission lethargy, seizures, and coma were present.

Physical Examination.—The child was deeply comatose and unresponsive to pinprick. Cheyne-Stokes respirations and complete dysphagia were noted. The tendon reflexes were hyperactive, with bilateral ankle clonus and Babinski signs. The spinal fluid showed a normal value for sugar, total protein of 53.6 mg. per 100 cc., and 420 lymphocytes per cubic millimeter.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—She showed evidence of returning awareness of her surroundings on the fourth day after admission, and she began to walk, holding onto furniture, on the 12th day but a month

later was still anxious to touch something to steady her gait. Speech began to reappear on the eighth day, but a month later it was still rarely spontaneous. Emotionally, she remained extremely unpredictable, with apparently unprovoked crying fairly frequently. Her usual reponse to suddenly presented suggestions was strikingly negative.

Seven weeks after onset she had recovered most of her motor function, though she was still weak and had rather lively tendon reflexes in her legs. Her speech was now fluent except for some slight slurring. She used her hands effectively but unsteadily. She was cheerful if left to her own devices and responded to a quiet regular routine, but became disturbed and resistant at minor changes. Her mood still varied suddenly; she turned rapidly from one activity to another and paid little attention to directions. On psychologic examination her reasoning and comprehension seemed intact. She had a good vocabulary and sentence construction, used adequate verbal patterns, but did not carry on much spontaneous conversation. She responded poorly to questions which called for immediate logical answers. Her drawings and copies of designs were irregular, at times adequate for her age, at other times poorly formed with perseveration in relation to one feature and showing lack of attention.

Eight months after her discharge from the hospital her mother reported that she had had innumerable temper tantrums, that she presented a serious feeding problem, and that she complained frequently of being overhot or very cold. Toward the end of the period she had begun to mingle with other children but got into many fights with them. Psychologic examination showed a willful, resistant, babyish child, with rather weak, unsteady movements. Cooperation could be obtained only with elaborate coaxing. Attention span and ability to copy designs were not improved as compared with results of examination at the time of discharge.

Fifteen months after discharge, when she was 5 7/12 years old, her behavior at home was more even, more cooperative, and somewhat more mature. The psychologic study now made it evident that she was not developing as well as she had prior to her illness. She was irregular and vague in her responses, did fairly well with questions which she could answer through the activation of previously learned associations, but did poorly when quick new judgments were required. In terms of quantitative tests, she had a mental age of 4 7/12 years, with an I. Q. in the range of 80 to 85. Her performances in attention tests, drawing, and form comprehension were on a 4-year level at best.

Three years after discharge, when she was 7 7/12 years, her mother found her easier to manage at home, though she continued to be willful and moody. She could get along well with a few children. Her school record was poor; she failed in the first grade, was put back into kindergarten, and was to reenter the first grade on trial in the fall. The psychologist described her as cheerful and talkative as soon as her mother was out of sight, but immature and dependent in the latter's presence. Her enunciation was poor, but her vocabulary was good. The content of her speech was immature, egocentric, and flighty. Her attitude toward her own achievement was improved; she was interested in trying and was occasionally tenacious in her effort to succeed. In terms of I. Q. she was still borderline, but form comprehension was poor. This was especially evident in the Kohs block design test, in which her mental age was less than 5 years. Her drawings showed lack of organization.

Five years after discharge, when she was 9 7/12 years of age, her behavior at home was in general more satisfactory. She was docile but nervous, bit her fingernails, and chewed her hair. She had failed the second grade. She was unable to get along with other children, who teased her. Psychologic examination found her friendly and cooperative, but shy. She was insecure about her achievements and found refuge in a dainty and doll-like attitude. She talked abundantly. After having given a solution to a problem, she would get carried away by associations to words or incidents referring to her own individual experiences. Her definitions showed interest in details and a lack of comprehension of the problem as a whole or of abstract ideas. Her procedure in block designs and object assembly was piecemeal and showed lack of comprehension of the structure as a whole. Her drawing continued to be sloppy and inaccurate. Her success in learning tests was very irregular and always meager (percentiles 0 to 25). On the Wechsler Intelligence Scale for Children she had an I. Q. of 70 to 75 on the total scale, an I. Q. of 80 on the performance scale, and an I. Q. of 70 on the verbal scale. An electroencephalogram was normal.

At this time the child's shortcomings had become clear. It was obvious that she required special class rather than grade teaching. The qualitative psychologic tests were clearly indicative of cerebral damage, though the quantitative examination showed nothing more specific than mental dulness.

The patient was the only girl in the family, her brother being nine years her senior, and her mother had even before the illness taken great pleasure in babying her. For instance, she had liked to wheel the child in the baby carriage and had fed her up to the time of the present illness. The child was obviously able and had attended an advanced nursery school with pleasure and success, beginning at the age of 3½ years. At the time of the illness, the patient's father was overseas in the armed forces, and the mother took great pleasure in the newspaper stories attendant on his return to the child's bedside at government expense and the consequent publicity about the illness. When the child was ready to be discharged home, her mother was so anxious about her that she preferred having her in a convalescent home for some weeks. During this time she seemed to enjoy several newspaper interviews relative to the child's slow recovery. Throughout her life, the mother, however, has enjoyed the child, finding great pleasure in her good looks, which she sets off admirably with pretty clothing. In spite of her ambitions, the mother has gradually accepted the fact that the child is "not like other children" and has given up her hope of sending the girl to a high-grade private school. Though the mother is greatly disappointed about the child's mental difficulties, she has, with some guidance, given the child protection, indulgence, and real affection, which seems to have allowed her "bad behavior" to improve, but which has not ameliorated the psychologic deficits.

Summary.—An able girl 4 11/12 years of age had measles encephalitis with characteristic spinal fluid changes and a prolonged course. Two months after the onset, qualitative psychologic examination suggested cerebral damage. At home, her mother at first treated her anxiously and tried to train her; obvious behavior problems appeared. With more understanding, the mother managed to keep the child's self-respect and affection intact, and she became easier to live with. As time went on, it became apparent that her cerebral damage was irreversible, but only three to five years after the illness did quantitative tests begin to give a measure of her psychologic deficits (Fig. 2).

CASE 5.—The father and mother of a girl 5 3/12 years of age (C. M. C. 277756) were living and well. There was at home one sibling, aged 9 years, who had not had measles.

Personal History.—The birth and neonatal history were unremarkable. At 3 months of age the child had thrombocytopenic purpura, manifested by hematuria and bleeding gums, but recovered in three months. She had mumps at 2 11/12 years and whooping cough at 4 years, without incident. She had been immunized to diphtheria in infancy and, in anticipation of entering school in the fall, had been vaccinated, unsuccessfully, at the age of 5 2/12 years. Vaccination was repeated 14 days prior to hospitalization, with primary "take" beginning 9 days prior to admission.

Present Illness.—The child was admitted to the Charles V. Chapin Hospital, Providence, R. I., with the following history: Five days before admission she had fever. Four days before admission rash developed which spread over the entire body and was diagnosed as measles. Three days and two days before admission she was better. One day before admission, headache, weakness, drowsiness, and incontinence supervened.

Physical Examination.—Physical examination on her admission to the Children's Medical Center showed a semicomatose girl who was delirious when aroused. The skin exhibited a fading macular hemorrhagic rash. Her neck was stiff. Kernig's sign was present bilaterally, and her tendon reflexes were sluggish. Her spinal fluid showed 200 cells, 90% lymphocytes, and a total protein of 400 mg. per 100 cc. Her white blood cell count was 20,000, with 85% polymorphonuclear cells.

Diagnosis.—The diagnosis was encephalomyelitis due to measles or vaccinia, or both.

Course.—She had an irregular fever (temperature elevation to 107 F.), had respiratory distress requiring use of a respirator, and was unable to swallow. Searching nystagmus, increased reflexes, and positive Hoffmann and Babinski signs, with contractures of the feet, developed in the first month. During the fifth week she began to follow objects with her eyes

and about six weeks after onset was obviously interested in persons who came and went. Two months after onset she was answering simple questions, but she still required tube feeding.

Three months after onset she was able to hitch about the floor on her buttocks, had little spontaneous speech, but answered simple questions with a bland facial expression. She could mobilize her previous stock of information in situations capable of immediate solution, such as counting, naming the members and pets of her family, and giving her address, but she had difficulty in thinking of the right word at the right moment of the conversation. She was very distractible and could not perform simple tasks requiring persistence or attention. She adjusted only with difficulty to new situations and was emotionally disturbed by unexpected shifts of activity or emotional attitude. She had no control of bowel or bladder function.

Four months after onset she began to walk alone. Eight months after onset she had bowel and bladder control and liked to play with other children.

A year after onset, at the age of 6 7/12 years, her speech was fluent and spontaneous, but she talked in free associations (of ideas) about her personal experiences and problems to a degree that suggested flight of ideas. In the psychologic examination her response was predominantly on the 5-year level (I. Q. of about 85). She was hasty and breathless in her approach and continued to be much better in tasks which could be performed immediately than in those requiring persistence and attention. Her form comprehension was poor, and she attached more importance to the details of a problem or figure than to the whole.

At home she was considered stubborn and restless, but it was felt she might be ready for a trial in kindergarten.

Two years after onset, when the child was 7 1/12 years of age, her mother reported that she had attended kindergarten during the previous year. She had been well physically, and the mother and the teacher agreed that her disposition had improved. At home, she was no longer difficult, the only complaint there being that she was too quiet and docile. She could play with other children but was often taken advantage of since she did not know how to defend herself. She continued to have a blank expressionless face and fluent speech, but she had learned to control her ideas, so that her conversation was more relevant and coherent. Her attitudes were still immature. In the psychologic tests she began almost any suggested task enthusiastically, but her interest and efforts soon faded. Either she continued automatically to do what she had begun or what was asked of her without paying attention, or her interest was easily distracted into a new line of thought. Her performances in the test situation, therefore, continued to be very uneven and, in terms of numerical results, at borderline level (I. Q. of 80 to 85). She was best in situations in which solution was quickly forthcoming on the basis of previously acquired intellectual patterns or information, and she frequently succeeded when a problem could be solved in one quick intuitive glance. She usually became emotionally upset and confused by any task requiring consistent planned activity over a long period. Occasionally she seemed rigid and compulsive and had difficulty in shifting from one task to the next.

Three years after onset, when the girl was 8 1/12 years of age, her mother reported that she was increasingly responsive, though still immature and puppet-like in her attitude. She had improved in daring, alertness, and observation. In the psychologic examination she was more controlled and careful in her working habits. On the Wechsler Intelligence Scale for Children she rated on the full scale an I. Q. of 75, on the performance scale an I. Q. of 80, and on the verbal scale an I. Q. of 75. The features noted on the previous examination were still present. She succeeded mostly in tasks calling for everyday comprehension and failed whenever organization of ideas was required. Her drawings showed disregard of spatial relationship and a tendency to concretize designs and to overemphasize details at the expense of the whole. Her learning ability was poor, as evidenced by a zero percentile rating in learning tests. Her electroencephalogram was normal.

Summary.—This little girl was four years younger than her only brother and the daughter of young, intelligent, emotionally stable parents. She was, before her illness, considered attractive, intelligent, and well equipped to enter kindergarten. She was obviously secure in her family relationships and made excellent adjustments outside. From the motor standpoint, she had been unusually capable and was considered a tomboy. She was described as easygoing, amenable, and seldom requiring reprimand.

Her mother wanted to assume responsibility for her care as soon as practicable after her illness and succeeded admirably. The parents have been able to face intelligently and kindly the problems that arose. They have accepted the child in each stage without frustration and have continued capable of explaining the genesis of her shortcomings to teachers and friends without too much difficulty.

The child so far has had to contend with very little pressure and has, on the whole, remained happy, though her intellectual accomplishments have steadily declined in relation to her advancing age.

CASE 6.—The family history of a girl 6 years of age (C. M. C. 335700) was not remarkable. The mother had had only the one pregnancy.

Personal History.—The personal history was not remarkable except that the patient had had many colds and several attacks of otitis media with purulent discharge. Development was stated to be average: She sat alone at 7 months of age, stood at 10 months, and walked at one year. The exact age of speaking was unknown. There was no history of convulsions or pica.

Present Illness.—Nine days before admission the patient had fever and anorexia. Onset of cough was eight days before admission. Seven and six days before admission she was better. Five days before admission a rash appeared in the mouth and on the skin. Fever was present. The diagnosis of measles was made. Three days before admission the child was up and out of bed, and the rash was fading. One day before admission headache and drowsiness were present, and she refused to eat or drink.

A lumbar puncture showed clear spinal fluid, with 26 white blood cells per cubic millimeter and total protein of 27 mg. per 100 cc. As symptoms continued to worsen, she was sent to the Children's Hospital for further care.

Physical Examination.—The patient was a critically ill, stuporous girl 6 years of age. When roused, she was completely irrational. The skin showed a fading macular eruption. The eyes had coarse random conjugate movements. The bladder was greatly distended to about 2 cm. above the umbilicus. Neurological examination revealed severe flaccid paralysis of legs, with absent tendon and plantar reflexes. The arms were stiff, with increased tendon reflexes. The abdominal reflexes were absent. There was no response to pinprick below the level of the 10th dorsal vertebra; above this level there was confused but immediate response. The white blood cell count was 20,000, with 60% polymorphonuclear cells. The spinal fluid showed a normal sugar level, total protein of 25 mg. per 100 cc., and 128 red blood cells and 28 lymphocytes per cubic millimeter.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—In the hospital the child remained confused and semiconscious for about a week, after which time her mental status slowly improved. As paralysis of the legs gradually diminished, a great deal of hyperesthesia was noted. At the time of discharge from the hospital, she was still very weak, but tendon reflexes could be obtained at the knees. Her bladder function was very much disturbed; after several catheterizations tidal drainage was used for a while, but at her discharge, two months after admission, urination was not reliably controlled. Her bladder became infected during her hospital stay, but the infection seemed well controlled with sulfadiazine therapy. The child was discharged in care of her mother, who was vastly overprotective and demanding.

When seen a year and a half later at the age of 7½ years, she was almost unapproachable because of fear and dependence on her mother. Her moods showed wide sudden swings. She preferred a crouching position and often voided on the floor. Her speech was voluble, but the ideas expressed were so loosely connected as to suggest a flight of ideas. Her reasoning ability seemed essentially on a 6-year level (the age at the time of the acute illness), but her thought processes were so disturbed by distractibility and attention to detail as to render them almost valueless for constructive thinking. It was felt that the patient had clear evidence of diffuse cerebral damage. Physical examination (report supplied by Dr. R. C. Eley) showed no neurological signs in relation to cranial nerves, arms, or upper trunk. Her lower adominal reflexes were not obtained, and her knee and ankle jerks were very feeble. Her rectal reflex was absent. She was greatly troubled by inability to move her bowels, and

impaction of feces developed and had to be relieved by oil enemata at intervals of weeks. Her urinary bladder tended to retention, apparently because of compression of the vesicle neck by impacted feces; at other times she appeared unaware of voiding and would wet her clothing. Her legs appeared of average strength, and her gait was normal. Her mother refused to have an electroencephalogram made.

Summary.—An average 6-year-old child acquired measles and on the eighth day encephalomyelitis, with definite spinal fluid pathology. The acute episode cleared slowly over a period of two months, and one and a half years later the girl still showed crippling psychologic and psychiatric defects. In addition, function of the spinal cord was also definitely defective. The mother, who was alternately demanding and overprotective, seemed unable to understand the child's disabilities. Impulsive and anxious behavior developed. The physician who cared for the child was uncertain how much her sphincter disturbance was reinforced by her emotional situation.

CASE 7.—The family history of a 6½-year-old girl (C. M. C. 340706) was not remarkable. There was one sibling, aged 2 years.

Personal History.—The personal history was not remarkable. Her development was thought to be normal. For two years the patient was in nursery school, which she enjoyed, and at the time of admission to the hospital she was doing well in the first grade. She had learned to read before she started first grade.

Present Illness.—Eleven days before admission the patient had cough and coryza. Ten days before admission a rash appeared. The diagnosis of measles was made nine days before admission. Eight days before admission her condition was improved, and it continued to improve until five days before admission, when she had recurrence of fever, with temperature elevation to 104 F. Penicillin was given. Four days before admission the body temperature was normal. Penicillin therapy was continued. Drowsiness, irritability, tenderness of the legs, loss of motion in the legs, and urinary incontinence were present. Stiffness of the neck appeared and became increasingly obvious. Intravenous administration of fluids was started and continued. There was gradual improvement, the patient taking sips of fluids by mouth and being moderately responsive until one day before admission, when drowsiness deepened to stupor. She was brought to the hospital because she was an impossible nursing problem at home.

Physical Examination.—The temperature was 98 F., the pulse rate 88, and the respiration rate 24. The patient was lethargic and dehydrated and responded only very slowly to painful stimuli. This slowness of response was present over the entire body. The skin showed fading, brown, macular blotches over the entire surface. Examination of the eyes revealed normal pupils and fundi. The tendon reflexes were hyperactive. Some weak active movement was seen in all extremities, with more activity on the right. Clonus and the Babinski sign were absent. Voluntary movement was everywhere tremulous. The spinal fluid showed a normal sugar level, total protein of 58.2 mg. per 100 cc., and no cells. The white blood cell count was 14,350, with 80% polymorphonuclear cells.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—She was treated with fluids intravenously and penicillin prophylactically. The next day she voided urine when placed on the bedpan and thereafter voided apparently voluntarily with this reminder. She remained semicomatose for about 10 days. The brisk reactions of her pupils, noted on entry, were no longer present on the fourth day. Her extremities became increasingly stiff over a period of days, and her tendon reflexes were lively, but clonus or the Babinski sign did not develop. About three weeks after admission she began to talk, though she still refused to eat or drink. At this time it became apparent that her vision was reduced to almost zero, and her optic disks were noted to be pale. Because of the difficulty in getting her to eat in the hospital, she was sent home in care of her mother six weeks after admission. At this time she was able to sit in a chair, talked freely, and readily activated previously learned ideas. She was, however, unable to think out new problems, and her sight was limited to finding and apprehending large bright objects, but her pupillary reaction to light had returned.

She began to walk about 8 weeks after discharge from the hospital, at first bumping into large objects, but at 10 weeks her sight had returned so that she could not only avoid furniture, find doors, and the like, but also recognize black and white pictures. Eleven or 12 weeks after onset she was able to play with other children, but she still tired easily if she met a large group. A psychologic examination showed her to be friendly but aloof, restless, and inattentive. She cooperated in only a few tasks and liked to change activities continuously. Her conversation was strikingly flighty and rambling. During the ensuing three months at home her behavior was unreliable and erratic; though previously neat, orderly, and well controlled, she would void in the middle of the floor or throw rocks and slap her brother when angry. Teachers at a parochial school were able to manage her for a few weeks, but she could not adjust to the discipline of the school as she had before and was withdrawn from it because of her unhappiness. At home, she could be maintained at a level of emotional serenity that was remarkable, apparently because of her mother's tolerance and affection.

Eighteen months after the onset of the encephalitis, at 7 1/12 years of age, her neurological situation was unremarkable. Vision was 20/20 in each eye, and funduscopic examination showed no abnormality. Psychologically the child was improved. Her speech tended toward a flight of ideas at times, though she could be controlled in this respect by a little guidance. She was easily diverted from any task by extraneous stimuli. Her learning was irregular, and she became easily confused. Her drawings were primitive and on the level of a 5-year-old child. Her difficulties were not described by her I. Q., which was 99 both in verbal and in performance fields, but were characterized by lack of mental control and perceptuomotor disturbances. She was able to attend the first grade in a small private school with an understanding teacher, who sent her on errands when she saw her getting restless or home in a taxi when she seemed to get tired and upset.

An electroencephalogram made at this visit showed a mildly slowed tracing, the rates varying from five to eight per second, with many four-per-second waves in the right occipital lead (Fig. 5).

Summary.—A 6 1/12-year-old child acquired measles and, on the seventh day of the disease, encephalomyelitis, with definite spinal fluid changes. Recovery from the acute phase was slow, and a year and a half later she still showed crippling psychologic defects and an abnormal electroencephalogram. Her psychologic status was still changing for the better, but the probability was that she would be left permanently more or less seriously damaged in spite of an average I. Q. In an affectionate and tolerant home, she has shown very few behavior problems after a short period.

Case 8.—The father and mother of a 6 7/12-year-old boy (C. M. C. 318539) were living and well. One older sibling had had measles two weeks before onset in the patient. Three other siblings had measles concurrently with the patient's attack.

Personal History.—The personal history was not remarkable. The child's development was average: He used single words at 12 months of age, walked alone at 13 months, and was doing well in kindergarten at the time of onset of the acute illness. He had many playmates and seemed socially well adjusted.

Present Illness.—Sixteen days before admission to the hospital fever and cough were present. Twelve days before admission a rash appeared. Six days before admission the rash was gone, and the patient seemed well. Four days before admission headache and weakness of the legs were present. Three days before admission he was unable to stand and was vomiting. On the day of admission the child was in coma with a generalized convulsion. There had been no fever since eight days before admission.

Physical Examination.—The patient was totally unresponsive. The eyes were fixed; the pupils were large and did not react to light. The throat and eardrum membranes were injected. The anterior cervical lymph nodes were enlarged. There were coarse rhonchi in the chest. No tendon reflexes were obtainable. No meningeal signs were present. The spinal fluid showed 1 lymphocyte and a total protein of 54 mg. per 100 cc. The white blood cell count was 24,150, with 70% polymorphonuclear cells.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—An electroencephalogram showed a grossly slowed rate, with the most marked change in the left occipital lead (Fig. 6, upper).

In the hospital he improved rather rapidly; within 24 hours he was sitting up and talking and was rational. His emotional status seemed appropriate. He did not have any tendon reflexes, though he voided adequately. Within a week his tendon reflexes returned, and he was discharged as apparently well on the 19th day after admission. An electroencephalogram made at this time was much improved, though still somewhat slowed and with left occipital focus.

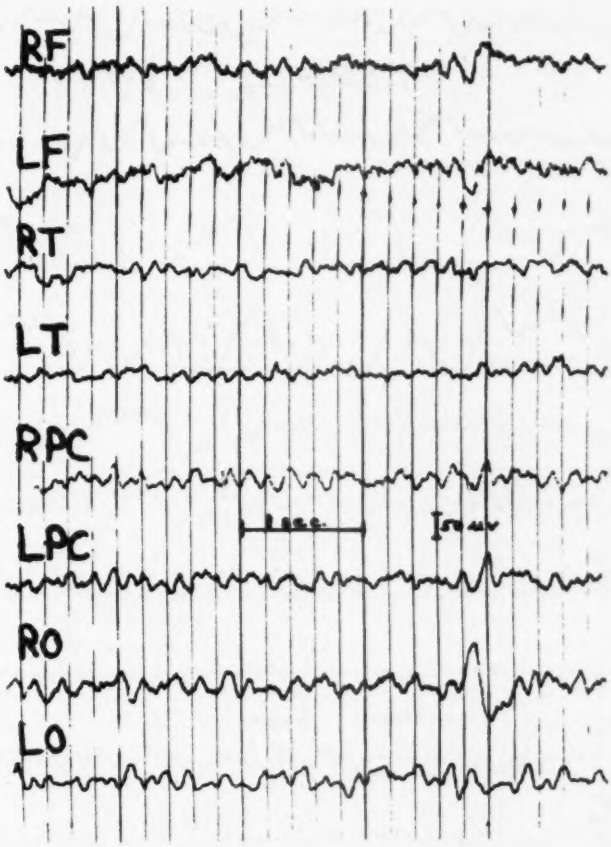

Fig. 5 (Case 7).—Electroencephalogram made at 7½ years of age, one and a half years after acute attack, showing mild slowing and slow spikes in occipital leads.

Two months later his mother thought him essentially recovered, though she noticed uncontrolled temper outbursts and occasional bedwetting. Psychologic examination showed some difficulty in form adjustment and in tests requiring "organized memorization" and persistent attention.

Three months later the slight defects noted above were diminishing. A year later psychologic examination showed him to have better-than-average ability, and he was doing well in school. His mother felt that he did not take teasing or see a joke as readily as the other members of the family did.

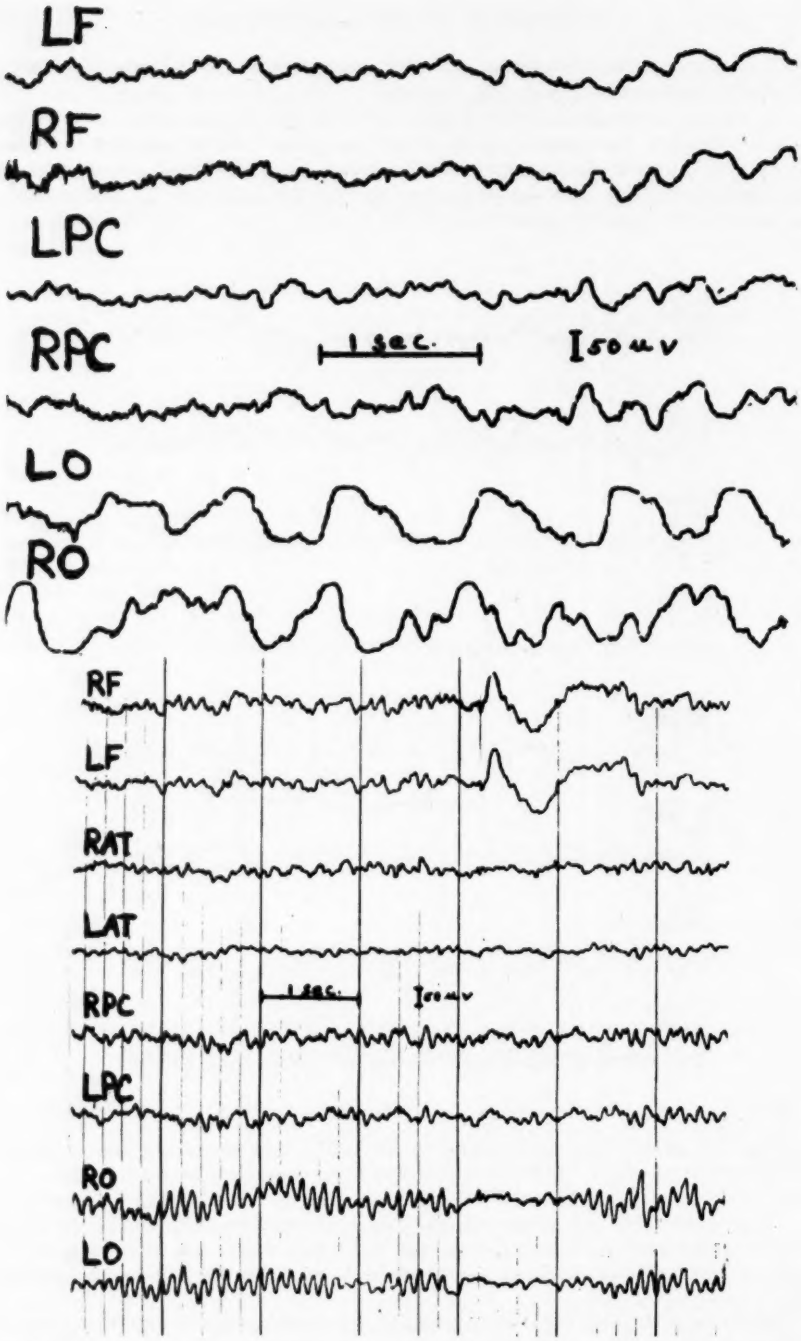

Fig. 6 (Case 8).—Upper, electroencephalogram made at 6½ years of age during acute attack of measles encephalitis, showing gross diffuse slowing, most marked in left occipital lead. Lower, electroencephalogram made at 9½ years of age, three years after acute measles encephalitis, showing occasional diphasic spikes in occipital leads.

Three years later, when the boy was 9 9/12 years of age, results of physical and neurological examinations were entirely unremarkable. Psychologically, he had superior intellectual ability, rating an I. Q. of 115 to 120 on the Wechsler Intelligence Scale for Children. The only possible deficits were his awkwardness in drawing and his relatively inferior visual memory. He had been promoted to the fourth grade. An electroencephalogram showed a rate of six to seven per second, with rare spikes in the right occipital and anterior temporal leads (Fig. 6, lower).

Summary.—An able 6-year-old boy acquired measles, and, 12 days after onset of fever, encephalomyelitis with minimal spinal fluid changes developed. His psychologic and neurological symptoms cleared in less than two weeks, and he has shown an orderly development since. At present, symptomless spikes in his electroencephalogram are the only abnormalities found.

CASE 9.—The mother of a boy 6 8/12 years of age (C. M. C. 294269) had mild diabetes.

Personal History.—The pregnancy was complicated by diabetes but was otherwise normal. Delivery was at full term with low forceps. The patient did well as a baby. His development was average: He sat at 8 months of age, walked at 13 months, and "talked early." He was in the second grade at the time of admission to the hospital.

Present Illness.—Twenty-two days before his admission cough, coryza, and fever were present. Eighteen days before admission a rash appeared. Thirteen days before admission he seemed well. Eleven days before admission headache, drowsiness, periumbilical pain, and vomiting without fever were present. The patient continued in same state to the time of his admission to the hospital.

Physical Examination.—The physical examination showed a listless boy who could be roused. His neck was stiff, and he had limitation of straight leg raising. Tendon reflexes were absent in the legs. His skin showed a fading, brownish rash, with branny desquamation and some dehydration. His spinal fluid contained 1 lymphocyte, and total protein was 19 mg. per 100 cc.

Diagnosis.—The diagnosis was measles encephalomyelitis, convalescing.

Course.—In the hospital he recovered rapidly, eating and drinking well. On the fifth day he was up and about, playing and talking normally. He was discharged in the care of his mother on the eighth day. When seen five years later, at the age of 11 9/12 years, he was well. He had had no unusual neurological or cerebral symptoms. He had been promoted annually in school and was an excellent pupil. He played baseball and football actively. Results of the general neurological examination were entirely physiological. The entire psychologic examination showed a boy with superior abilities, the results on the performance tests being even better than the excellent results on verbal tests. An electroencephalogram revealed a few bursts of rather high-voltage 5-per-second waves in the frontal leads, with a background rhythm of 9 to 10-per-second waves. Overventilation produced a large build-up in the frontal waves. The electroencephalogram was thought to be within normal limits.

Summary.—An able child had probable encephalomyelitis approximately a week after the onset of measles. He was admitted to the hospital in the convalescent stage and recovered rapidly. His intellectual and personality development has continued at a very satisfactory rate since this episode.

CASE 10.—The father and mother of a 6 7/12-year-old boy (C. M. C. 352352) were living and well. One older brother had had measles beginning 20 days prior to the patient's admission to the hosptital.

Personal History.—The pregnancy was complicated by excessive vomiting, poor diet, hypertension, and edema. The birth weight was 8 lb. 15 oz. (4,058 gm.). There were no neonatal complications. The patient sat at 8 months of age, walked alone at 14 months, and talked at 15 months. He was in the first grade at school and doing well. He had had no serious illnesses or convulsions. He had always been "nervous and restless."

Present Illness.—Fourteen days before his admission to the hospital, because of his brother's measles and six days after onset of the brother's coryza, the patient was given 0.75 cc. (or 0.014 cc. per pound [0.5 kg.] of body weight) of gamma globulin. Eight days before admission he had cough, coryza, and mild prostration, to which was added a temperature elevation to 102 F. Five days before admission a rash appeared on the face and on the next day spread

to the trunk. Three days before admission the rash reached its greatest intensity. Two days before admission the child felt better, and the rash began to fade. Twelve hours before admission he had a short convulsion, after which he was limp and out of contact for two or three hours. On recovering consciousness, he complained of severe headache and was listless. Two hours before admission he had a severe convulsion lasting 10 minutes, since which time he had not been clearly conscious.

Physical Examination.—The patient was a well-developed and well-nourished boy who was semiconscious, at times screaming shrilly in apparent fright, at other times lethargic and difficult to rouse. The skin showed a brownish, profuse, maculopapular rash of rather wide distribution. No abnormal neurological or meningeal signs were elicited. His white blood

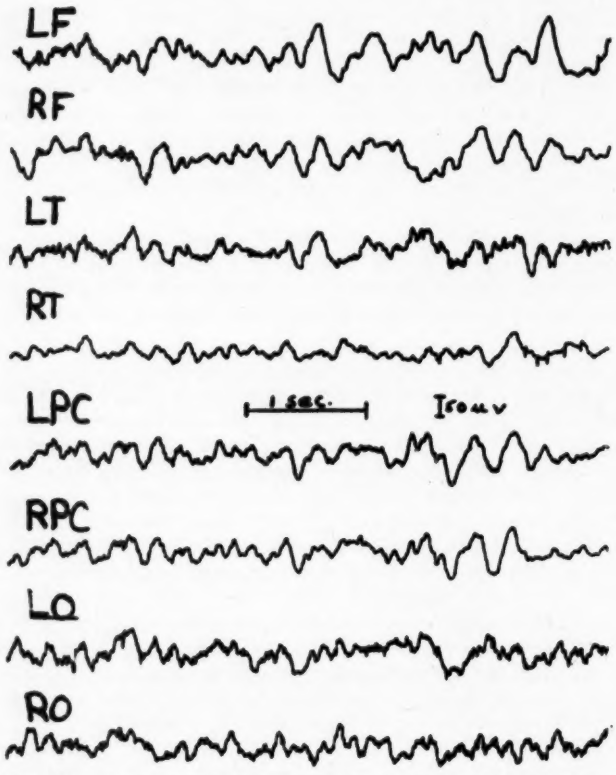

Fig. 7 (Case 10).—Electroencephalogram made at 6½ years of age, during acute attack, showing diffuse slowing.

cell count was 18,900, with 71% polymorphonuclear cells. The spinal fluid showed 46 white blood cells, of which 80% were lymphocytes, a total protein of 42.6 mg. per 100 cc., and a qualitatively normal sugar level.

Diagnosis.—The diagnosis was measles encephalitis.

Course.—An electroencephalogram made five days after admission showed a background rhythm of four to six per second with many two and three-per-second waves, especially in the precentral leads, and a large build-up with hyperventilation. This activity was regarded as abnormally slow (Fig. 7). In the hospital he remained drowsy and irritable, with a tendency toward confusion for two days, but his symptoms rapidly cleared, and in four or five days after admission he seemed on casual observation to have recovered.

In the next three months, however, with a home teacher, his ability to learn new material was very limited, and if put under stress to learn he became emotionally disturbed and desperate.

Seven months after admission, in spite of an I. Q. of 110 and the efforts of a home teacher, he had learned no new material and had not regained what he knew before. He showed more reversals in relation to writing and drawing than was apparently the case prior to his illness and was still easily fatigued when faced with tasks requiring persistent attention. Though socially he appeared to have recovered, he obviously required tolerance on the part of adults

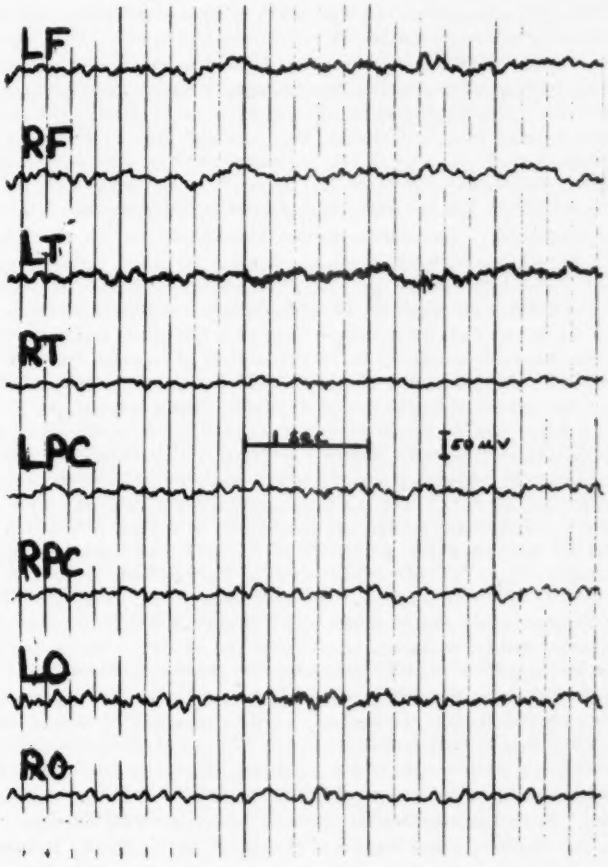

Fig. 8 (Case 10).—Electroencephalogram made six months after acute attack, considered normal.

and parents, and the teacher agreed that he should repeat the first grade. An electroencephalogram was normal (Fig. 8).

Summary.—A 6½-year-old boy had average measles six days after receiving 0.014 cc. of gamma globulin per pound of body weight. On the ninth day of the disease encephalitis with striking spinal fluid pathology developed, the acute symptoms clearing rapidly. In the seven months since discharge he has, however, had difficulty in learning new material, and he has even retrogressed in his ability to perform tasks requiring spatial orientation. Easy fatigability has been a major handicap. He is still improving.

CASE 11.—The father, mother, and one older sister of a girl 7 2/12 years of age (C. M. C. 300434) recovered from probable measles one week before the patient's admission to the hospital.

Personal History.—The personal history was not remarkable. There was no history of convulsions, pica, or head injuries. Her development was average. She was in the second grade and doing well at the onset of the present illness.

Present Illness.—Six days before her admission to the hospital the child was feverish. Five days before admission Koplik spots were noted by the physician, and the child was given 4.5 cc. of gamma globulin intramuscularly. Four days before admission a generalized rash appeared. Two days before admission the patient improved in general symptoms, but because of cough sulfonamides were given. One day before admission abdominal pain, difficulty in voiding, listlessness, and drowsiness appeared.

Physical Examination.—The patient was a listless and drowsy girl who was easily aroused and well oriented when aroused. The skin showed fading brownish macular rash. The mouth had small hemorrhagic spots on the buccal and gingival mucosa. Examination revealed many coarse and medium moist rales in the lungs. The neck and back were supple. The tendon reflexes were physiological. The bladder was not distended. The white blood cell count was 13,600, with 73% lymphocytes. The spinal fluid showed a normal sugar level, a total protein value of 36 mg. per 100 cc., and 156 white blood cells per cubic millimeter.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—In the hospital her drowsiness diminished rapidly over a period of three or four days. She had considerable difficulty in voiding; in the first few days her bladder reached the umbilicus before she could empty it. No weakness of the legs or trunk was noted at any time. She was discharged from the hospital a week after admission, apparently recovered.

A month later psychologic examination showed a child of superior ability, who did well in situations to which she was already accustomed, but she tired relatively easily in trying to learn new material and to synthesize new ideas. Eight months later results of psychologic examination were not quite so satisfactory. She had difficulty in tasks requiring persistent attention; her drawings were poorly organized in direction, and her memory for design was poor. She was repeating the second grade on advice given at discharge and was doing well.

Four years later, at the age of 11 9/12 years, she was doing well, but had little competition in a small country school. Her concept formation and ability to express herself were moderately inadequate, but her learning ability, attention, and emotional state seemed average. On the Wechsler Intelligence Scale for Children she scored on the total scale an I. Q. of 105, on the verbal scale an I. Q. of 95 to 100, and on the performance scale an I. Q. of 110. At this time an electroencephalogram showed a background rhythm of 9 to 10 per second, with runs of 4- to 5-per-second and low-voltage 12- to 15-per-second activity. Diphasic spikes were seen occasionally in the right occipital lead. The record was considered abnormal.

Summary.—A 7 2/12-year-old girl acquired measles, with drowsiness and urinary difficulty on the fifth day of the disease. No weakness of the extremities or sensory changes were elicited. Her spinal fluid showed marked pleocytosis and mildly elevated protein value.

Recovery from her acute symptoms was rapid, and four years later she was practically recovered, though she showed minor psychological abnormalities suggestive of mild diffuse cortical damage. An electroencephalogram tended to substantiate these findings.

CASE 12.—The family of a girl 7 3/12 years of age (C. M. C. 282306) included one uncle with epilepsy.

Personal History.—The child's development was rapid. She took steps alone and spoke words at 10 months of age. She had always done well in school and was in the second grade. She had had an attack of febrile illness with coryza and rash one year prior to hospitalization, at which time a diagnosis of measles was made. The past history was otherwise not remarkable.

Present Illness.—Seven days before admission to the hospital the patient had a temperature of 101 F. Six days before admission coryza, malaise, and photophobia were present. Five days before admission, a rash appeared on the face and spread to the body. A cough and temperature elevation to 104 F. were present. Four days before admission, the temperature decreased gradually and the rash was fading. Three days before admission the child had a

recurrence of temperature elevation, with drowsiness and brightening of the fading rash. Two days before admission she had periods of excessive somnolence, confusion, hallucinations, stiffness of the neck, urinary incontinence, and temperature increase to 100 to 101 F. One day before admission the patient was in a deep coma from which she could not be aroused.

Physical Examination.—On physical examination a brownish, red, maculopapular rash with fine desquamation was apparent. The patient was in deep coma with no response to painful stimuli. There were roving movements of the eyes. Respirations were shallow and mostly abdominal. There were sluggish tendon reflexes in the arms, absence of tendon reflexes in the legs, and no response to abdominal or plantar stimulation. In addition, the usual physical signs of pneumonia were present over the lower lobe of the right lung. Her white blood cell count was 35,000, with 92% polymorphonuclear cells. Her spinal fluid showed a total protein of 41 mg. per 100 cc. and 100 cells, all of which were lymphocytes.

Diagnoses.—The diagnoses were measles encephalomyelitis and bronchopneumonia.

Course.—She was maintained with fluids given subcutaneously and sulfadiazine for 2 days, then given feedings by gavage for 15 days, after which she began to eat and to move her arms well. She began to use words on the 16th day and was talking well on the 26th day, at which time she also got spontaneously to a sitting position, though she did not move her legs. Strength returned slowly in her legs, so that she was able to walk with help by the 40th day, and on the 50th day she was running about the ward, though with an awkward gait. She was, however, incontinent of urine unless toileted by the clock. Psychologically, she showed easy fatigability, but function and attention were good for her age, though she was still easily excited. A program in school and home allowing for these disabilities, and starting with repetition of the second grade, was arranged with the help of her mother.

Psychologic examinations showed easy fatigability in the first three years after discharge, with extremely marked tension and restlessness, but she always seemed to be a capable, rather precocious girl. Her I. Q. remained steadily at 125, and her schoolwork was in consonance.

At 13 years of age, six years after the acute illness, she continued as a fully responsible person. Urinary incontinence was the main complaint; she had to go to the toilet regularly and control her fluid intake sharply. At night, she had to use an alarm clock to awaken her for voiding every four hours, or she wet the bed. Her legs had progressively improved in strength over the years, so that now she measured improvement in terms of the latest mountain she had climbed. A general neurological examination showed no abnormalities, normal tendon reflexes in the legs, and normal rectal sphincter reflex. A urine sample was entirely normal. An electroencephalogram showed low-voltage fast activity, with some 9- to 10-per-second waves in all leads, and was considered normal.

Summary.—An able 7-year-old girl had measles, complicated by encephalomyelitis, with typical spinal fluid pathology, and pneumonia on the fifth day of illness. Within a month she had recovered to her previous intellectual level, but intellectual fatigue remained prominent for three years. The evidence of myelitis cleared slowly. At present, she is intellectually competent, emotionally stable, but still unable to control her bladder over the usual span of time.

Case 13.—The father, mother, and three siblings of a 7 11/12-year-old girl (C. M. C. 330716) were living and well. There had been no deaths or miscarriages.

Personal History.—The patient had no important illnesses, convulsions, or trauma. Developmentally, she sat at 5 months of age, stood at 12 months, walked at 14 months, had bowel control at 9 months, and complete sphincter control at 2 years. She was in the fourth grade in school and was doing well at onset of the present illness.

Present Illness.—Ten days before her admission to the hospital cough, coryza, fever, and vomiting were present. Seven days before admission a measles rash appeared on the skin. Six days before admission the rash was well developed. Five days before admission the patient was moaning and crying out in her sleep. She talked irrelevantly from time to time, though she knew members of her family. Duracillin® (a preparation of procaine and penicillin G in sesame oil) was given because of a chest infection. Three days before admission her condition was about the same. Two days before admission she seemed better oriented, but her speech was difficult to understand. That night she tried to get out of bed but collapsed on the floor. On the day of admission she was very disoriented, plucking objects out of the

air, screaming, and frightened, and then rather rapidly she became unresponsive and semicomatose. She would rouse from her lethargy for a moment if stimulated painfully.

Physical Examination.—Her temperature was 98.6 F., the pulse rate, 120, and the respiration rate, 30. The skin showed a blotchy, bronze macular rash with fine desquamation. The skin and mucous membranes were dry. Her neuropsychiatric status was as follows: She was semiconscious, but could be roused when stimulated painfully. She screamed and garbled incoherently. When unstimulated, she lay almost motionless except for her eyes, which continually moved about as if looking for something. The tendon reflexes were all lively. Presence of the Babinski sign was doubtful on both sides. The white blood cell count was 11,500, with 75% polymorphonuclear cells. The urine and spinal fluid showed no abnormalities.

Diagnosis.—The diagnosis was measles encephalitis.

Course.—A roentgenogram of the chest showed questionable consolidation in the upper lobe of the right lung. She was hydrated with dextrose and water given intravenously and was treated with penicillin and sulfadiazine, though she had little or no fever. For the next two days she was less lethargic but carried on conversations with persons who were not present and was very frightened when roused. An electroencephalogram made on the fourth day in the hospital showed a rate of four to six per second, with many 2- and 3-per-second waves in all leads, and was considered to be diffusely and grossly slowed (Fig. 9, upper). After that her condition improved rapidly, and she was returned home on the 11th day after admission, apparently herself.

A week later the mother reported that the child was her usual self except that she tired easily. An electroencephalogram made two months after discharge showed normal rates, with spikes in the right temporo-occipital areas. She returned to school in the third grade the following year and received honor grades in all subjects.

Two years after discharge results of her neurological and physical examinations were normal. Psychologically, she had superior intellectual ability, with an I. Q. of 125, and no apparent irregularities, though a year before she had shown some difficulty in learning rather complex new material. Her electroencephalogram was entirely normal (Fig. 9, lower).

Summary.—A rather able child 7½ years of age acquired measles, with encephalopathy developing on the fifth day of the disease. Within three weeks from the onset of this disease the child seemed herself again save for easy fatigability. Since that time she has continued to show superior intellect and a good personality.

CASE 14.—The father, mother, and one sister, aged 11 years, of a boy 7 11/12 years old (C. M. C. 306097) were living and well.

Personal History.—The pregnancy, neonatal period, and infancy were normal. His development was average. He walked at 14 months of age and had words at 12 months. He had just finished the second grade and had been promoted to the third grade prior to the present illness. Schoolwork was easy for him. He had had a fair number of illnesses, including mumps at 4 years and tracheobronchitis at 5 years of age, for which he received large doses of some sulfonamide drug. He had the usual prophylaxis against diphtheria, whooping cough, and smallpox, without incident. There had been 18 cases of measles in the patient's class at school in the previous month.

Present Illness.—Seven days before admission to the hospital he was feverish and irritable. Six days before admission, a rash appeared on the face and a diagnosis of measles was made. Four days before admission, the patient was better and the rash was fading. Three and one-half days before admission he was irritable, feverish, and sleepy. Three days before admission a diagnosis of bronchopneumonia was made because of more cough and a temperature elevation to 102 F. He was given sulfadiazine, 0.6 gm. eight times a day, and penicillin, every two hours orally. Cough and fever were gone in 12 hours, but the boy was still lethargic and cried when touched. Two days before admission his lethargy deepened, and the neck was stiff. No fever was present.

Physical Examination.—The patient was confused and disoriented. He talked incomprehensibly when roused and then lapsed into stupor. He was generally hyperesthetic when handled. A fading brownish macular rash was present, with a fine branny desquamation. Fading Koplik spots were noted in the mouth. There were continuous coarse, wandering,

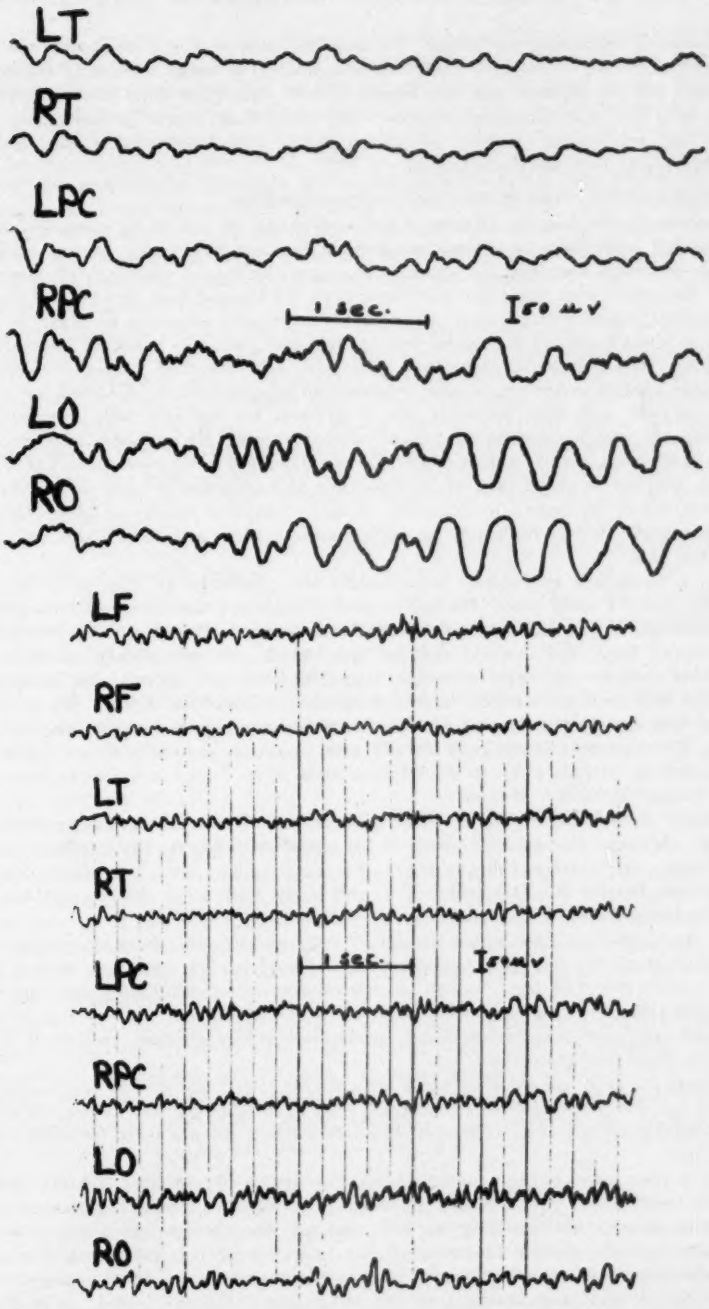

Fig. 9 (Case 13).—Upper, electroencephalogram made during acute measles encephalitis, showing diffuse gross slowing. Lower, electroencephalogram made at 9 years of age, two years after attack. Normal tracing.

uncoordinated extraocular movements. The neck and back were stiff on flexion and painful. Straight leg raising was sharply limited on both sides. The tendon reflexes in the legs were increased, and the Babinski sign was elicited on both sides. The white blood cell count was 9,300, with 55% polymorphonuclear cells. The spinal fluid showed a qualitatively normal sugar level, total protein of 54 mg. per 100 cc., and 62 white blood cells per cubic millimeter, of which nearly 100% were lymphocytes.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—In the hospital, because of profound stupor, he had to be gavage-fed for four weeks after admission. On several occasions in the first two weeks, he was catheterized because of urinary retention. He began to respond and to answer questions with single words about five weeks after admission. Contractures of the hip and knee flexors and a tendency to decubitus complicated his care. About eight weeks after admission he began to use his hands to feed himself and to examine toys; at this time tremor on voluntary innervation was prominent. His extraocular movements were now well controlled. About 10 weeks after admission athetoid movements became prominent on voluntary effort. He could get from his bed to a chair with help. He could talk in sentences but had very little spontaneous conversation. He remained passive and seemed remote and inert. He was noted to be emotionally labile, cried easily, and had a tense laugh. He was discharged to his mother's care at that time.

The tendency to contractures of his knees and hips continued at home and prevented his standing, and by 16 weeks after admission, in spite of physical therapy at home, contractures had developed. He was readmitted for application of traction and casts, which his skin now tolerated well.

On a psychologic examination seven months after discharge, he tried to be cooperative but this required much effort. He had a nervous laugh and was ill at ease throughout the examination. He was very slow and hesitant in his approach, as well as in his responses. He still seemed foggy and confused with all tasks which were not already familiar to him. While he remembered simple arithmetic facts and knew how to print his name, he had difficulty with writing it—a skill he had acquired just before his illness. His solutions to several easy and short reasoning problems were adequate enough but cost him an obvious effort. He rated zero percentile in learning tasks requiring acquisition of new material, but he reached an average I. Q. on the Stanford-Binet tests, though he failed on some of the items because of his lack of speed.

Fifteen months after discharge from the hospital his motor situation had improved to an average efficiency. He had some tremor in his hands. At home, he was described as restless and bored, never staying with any activity for any length of time, and not knowing what to do with himself. He still preferred to stay away from other children and was easily upset and irritable when in company.

In the psychologic examination he seemed self-conscious and lacking in confidence. He was timid in starting new tasks. Learning had improved but was slow and required a great deal of effort that tired him. Though his performances in reasoning tasks gave him average numerical rating, the quality of many of his performances was poor. He was apt to get lost in details and forget to appreciate all the factors involved in a situation. He became disturbed when he found himself confused.

During the next year the child had a home teacher who found that he progressed, though he still was slowly reconquering second-grade work. The following year he returned to school in the third grade, got along reasonably well with children, but was noted for quick emotional outbursts.

Three years after discharge the psychologic examination showed great progress. Emotional outbursts and lack of judgment had diminished. He still seemed to lack confidence, tried to remain passive, and avoided being caught in mistakes. He was slow and hesitant when faced with new tasks and shunned situations in which he had to use independent judgment. On the Wechsler-Bellevue Intelligence Scale he rated on the full score an I. Q. of approximately 95; on the performance scale, an I. Q. of 105, and on the verbal scale, an I. Q. of 85 to 90.

Four years later, at the age of 12 years, he had completed the fifth grade and was promoted to the sixth grade; his school marks were A in conduct and spelling and B and C in all other subjects. His family was satisfied with his progress and found him agreeable and well

adjusted at home. There were no more complaints of impulsive behavior either at home or in the neighborhood. He was described as rather quiet, passive, and somewhat dependent, easily sensitive and insecure. In the psychologic examination he rated on the Wechsler Intelligence Scale for Children on the full score an I. Q. of 110; on the performance score an I. Q. of 125-130, and on the verbal score an I. Q. of 95. His learning ability had improved except for some slowness in memory for designs. He seemed aware of his limitations in speed and perceptive abilities. The most outstanding characteristics in this examination were his hesitant and overcautious approach, his desire to avoid spontaneous decisions, and some difficulty and reluctance in expression of his ideas. He tried to secure detailed, concrete explanations for any new tasks, made sure he understood what was asked of him, and disliked venturing into experimental situations. With such habits and attitudes, he was able to master his present life situations creditably.

Summary.—An 8-year-old boy had measles and probable pneumonia, with appearance of encephalopathy on the fourth day of the disease. His spinal fluid showed characteristic changes. His course was protracted; he was discharged from the hospital two months after admission, still unable to walk, with limited speech and contracture of limbs. Recovery has continued over the entire observation period of four years. At first, mental fogginess, timidity, and emotional instability were so marked as to prevent any adjustment to new situations and ideas. He was protected by a home teacher. Over a four-year period, these difficulties have improved to the point where he can compete, though mild psychologic variations and an emotional restriction remain (Fig. 10).

CASE 15.—A boy 8 years old (C. M. C. 271093) was admitted to the hospital with the chief complaints of coma and fever of three days' duration.

Family History.—The mother and father were living and well. There were four siblings, 16, 13, 11, and 9 years of age; all had had measles several years previously. The father and three of the siblings had difficulties in school because of inability to learn to read.

Personal History.—The child's personal history was not remarkable. There had been no convulsions, pica, severe reactions to inoculations, or head trauma. Development was considered average: He went to kindergarten at 5½ years of age and entered first grade at the age of 6½ years. At the time of hospitalization he was doing excellent work in the second grade, and an intelligence test at school was reported to have shown an I. Q. of 120 to 130. As the youngest member of the family, he had been considered stable, good-natured, and able to take care of his interests without getting angry. Cases of both measles and rubella (German measles) were present in school.

Present Illness.—Ten days before admission the patient had fever, rash, and cough. Nine days before admission the fever was abating. During the succeeding week the child did not feel well and remained in bed. The cough and rash gradually subsided during this time. Three days before admission vomiting, fever, and disorientation were present. Two days before admission there were coma, rigidity, and temperature elevation to 103 to 105 F., which continued to the time of admission.

Physical Examination.—The patient was in a deep coma, with rigidly extended arms and less rigidity of the legs. There was slight squirming on painful stimuli, occasionally. The skin showed a fading, bronzed macular rash, with rare fading petechiae. Examination of the eyes revealed full retinal veins. The tendon reflexes were normal throughout, but the Babinski sign was present bilaterally. The respirations were stertorous. His spinal fluid showed 80 lymphocytes per cubic millimeter and a total protein of 31 mg. per 100 cc.

Diagnosis.—The diagnosis was measles encephalomyelitis.

Course.—Gavage feedings and suction drainage of the nasopharynx were required for two weeks, with no sign of returning consciousness. After that, he began to open his mouth for a spoon and responded to questions with grunts; by the fourth week he was fed entirely by spoon. Six weeks after admission, over a period of a few days, he sat up, began to talk in sentences, stood, walked, and used simple toys. He went home in care of his mother at this time, on her insistence, in spite of the advice of the psychologist and physicians. There, he was in constant turmoil; for instance, he demanded his lunch a few minutes after finishing it and denied having had it. In spite of his obvious inability to concentrate, his mother sent him back

to school in the third grade, as his teacher had promoted him during the summer. His teacher was unable to keep his attention and by the end of the year recommended withdrawal from school.

Five months after onset, his speech was voluble and poorly controlled in content. He could read a few simple words but got lost in sentences; picking a single word and disregarding the rest of the sentence, he would embark on a free association of ideas. He could not write his name reliably because of perseveration in letters. When asked what he would do if, on the way to school, he found himself in danger of being late, he replied, "I'd climb up into trees and go behind houses." Asked why, he said, "Well, of course if I was in danger. . . ."

Ten months after discharge he was restudied in the hospital and showed a large degree of recovery. His electroencephalogram exhibited much 20- to 25-per-second activity at rather high

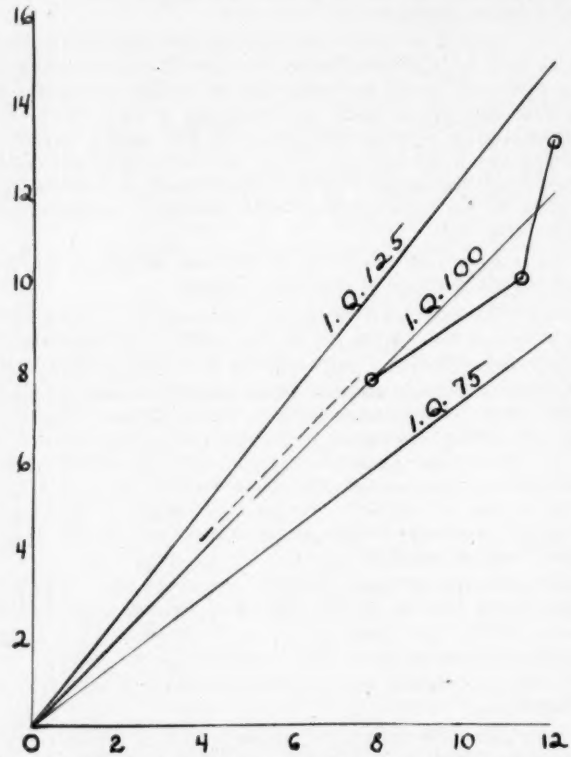

Fig. 10 (Case 14).—Graph describing recovery in terms of global scores. Because of patient's learning and attention deficits, his I. Q. gradually fell to a general level of 95 during first three years of his illness. At this time, however, it was apparent that his psychologic function had improved from qualitative point of view, and a year later this was reflected by his superior achievement in terms of I. Q.

voltage and was considered probably abnormally fast. His attention spans were fair; his perceptuomotor difficulties had largely disappeared, and his hands showed no tremor. His reading, however, was very poor. He had large gaps in his school learning. He had a remote and mask-like attitude. Although doing relatively well with individual adults, his behavior in a group was difficult, aggressive, and impulsive.

Two years after discharge his reading defect was outstanding, but, in addition, his drawings were crude and infantile, and, in spite of an I. Q. of 110 to 115, he was not learning in school. His attention was fair. His behavior became increasingly impulsive and impatient, and, finally, three years after discharge he was excluded from school for throwing a knife at a teacher.

In the previous summer he was dismissed from camp for cruel, impulsive behavior to the other children and for kicking the camp director. He was an outcast in his neighborhood.

Summary.—An 8-year-old boy who had been doing well in the second grade, living in a rather disorganized impulsive family, many of whom did not get far in school because of reading difficulties, had measles encephalomyelitis with a protracted course. After he regained consciousness, his intellectual processes were confused for many months and he had great difficulty with attention and perceptuomotor function for about a year, but thereafter he improved so that on psychologic tests he gave good performances, save in reading. During this interval he had been expected to live up to his previous promise and was left mainly to his own devices. His behavior became increasingly impulsive and surly, and, finally, he was dismissed from camp and excluded from school on this account. In a disorganized family his reaction to the burden put upon him during his convalescence seemed to have stimulated a response of antagonism which now colored his entire personality. These difficulties were not paralleled by psychologic findings at the last examination. How to apportion them among hereditary factors, stresses imposed on him during a period of intellectual disability, and general environmental disorder was an impossible problem.

CASE 16.—The father and mother of a 10½-year-old boy (C. M. C. 340722) were living and well. One sibling, three years younger than the patient, had had measles two weeks before the patient was admitted to the hospital.

Personal History.—The personal history was unremarkable. His development was more rapid than average. The mother did not remember the dates of walking or talking. The patient was in the fifth grade and doing well at the time of illness. He had had no important previous illnesses, operations, trauma, or pica. He had had no convulsions previously.

Present Illness.—Seven days before admission, and seven days after appearance of the sister's rash, the patient had fever and cough. Four days before admission, his temperature rose to 105 F. and his cough was worse. Three days before admission a typical measles rash appeared all over the body. Two days before admission the temperature was normal. One-half day before admission he was lethargic and had a headache but no fever. Two hours before admission he had a generalized convulsion.

Physical Examination.—The temperature was 100 F., the pulse rate 100, and the respiration rate 36. He had a generalized convulsion with total unconsciousness. The fundi showed one small hemorrhage in each retina and a subconjunctival hemorrhage in the right eye. The skin exhibited brownish fading maculopapular rash, and the mouth showed roughened buccal mucosa. The neurological examination disclosed normal tendon reflexes and no signs of involvement of the spinal tracts. The white blood cell count was 16,700, with 75% polymorphonuclear neutrophiles. The spinal fluid showed a qualitatively normal sugar level and a total protein of 99.4 mg. per 100 cc., with 72 white blood cells per high-power field, of which 96% were lymphocytes.

Diagnosis.—The diagnosis was measles encephalitis.

Course.—With sedation, the convulsions subsided fairly rapidly, and 36 hours after admission the patient was talking and recognized his parents, though he was still confused, belligerent, and overactive. Four days after admission he was reading comic books with interest, and he was discharged 10 days after admission apparently well, except for a slight right internal strabismus.

When seen on follow-up examination a year later, he showed some personality difficulties, mostly in the family setting, such as belligerence, withdrawal, and shyness, but these seemed to be in consonance with the rigid demands of his parents. Psychologic examination showed, on the Wechsler Intelligence Scale for Children, an I. Q. of 118 on the total scale, an I. Q. of 106 on the performance scale, and an I. Q. of 130 on the verbal scale. It seemed possible to explain this discrepancy on the two scales as a sign of mild cortical damage, but the evidence seemed strongly in favor of explaining it as of congenital origin. His schoolwork in the sixth grade was good.

Summary.—A boy 10½ years of age had an encephalopathy characterized by convulsions, coma, and mental confusion on the seventh day of measles. His spinal fluid showed an abnormal increase in lymphocytes and total protein. After four days of mental symptoms, he recovered rapidly, and a year later no certain evidence of his encephalopathy remained.

TOXOPLASMOSIS

Methylene-Blue Dye Tests and Mouse-Antigen Skin Test in One Hundred Two Hospitalized Children

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A REQUEST was received in 1950 for blood sera of infants and children as a part of a national survey concerning the incidence of toxoplasmosis being conducted by Feldman. As a consequence, 47 blood samples were obtained from infants and children in the clinics and wards of the Charity Hospital of Louisiana. These specimens were collected on a single day, and the patients were selected only in that they were not suspected of having toxoplasmosis. The results of the methylene-blue dye test performed on the sera by Dr. Feldman [1] were most startling in that the sera of 25% of the children in the age range of 0 to 19 years showed positive titers and that, further, in the 5- to 9-year age group 43% of the children tested had positive titers.[2] It was further significant that most of these children had titers of 1:16 or higher, suggesting the possibility of acquired postnatal toxoplasmosis, rather than congenital infection. Elaboration of the initial study was accomplished in the following year (1951) and included increasing the series to approximately 100 subjects, perusing the medical records of each patient for possible toxoplasmosis, reexamining for signal physical evidence any patient concerning whom question arose, and performing Toxoplasma skin tests on as many patients as possible. Again, the dye tests were performed in Feldman's laboratory. The skin testing was accomplished with material prepared from mouse peritoneal exudate according to the method of Frenkel.[3] The antigen was injected intradermally in the skin of the left forearm.[4] A control injection with mouse spleen was similarly made in the right forearm, and readings were made of both sites at 24,

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1. The studies on toxoplasmosis performed in Dr. Feldman's laboratory were supported by a Grant-in-Aid from the National Institutes of Health.

2. In this paper "positive" refers to methylene-blue dye-test titers of 1:4 or higher.

3. Frenkel, J. K.: Pathogenesis, Diagnosis and Treatment of Human Toxoplasmosis, J. A. M. A. **140**:369, 1949.

4. The skin-testing material was furnished by Dr. C. E. Roach, of the Eli Lilly & Company Research Laboratories.

48, and 72 hours. An area of erythema or induration of over 10 mm. in diameter was considered a positive reaction if it persisted for 72 hours and if no such area occurred at the site of the control injection.

The investigation was planned with three objectives in mind: first, to elucidate further the incidence of toxoplasmosis in the New Orleans area; second, to correlate the dye and the mouse-antigen skin tests, and, finally, to evaluate the presence or absence of specific clinical evidences of disease with these laboratory determinations.

The first instance of human infection with Toxoplasma was described by Janku in 1923.[5] The third case, but the first in the United States, was reported by Wolf and Cowen in 1937.[6] These early cases, like the majority subsequently reported, were of the congenital type, with extensive lesions of the nervous system producing such classic signs and symptoms as hydrocephaly, chorioretinitis, cerebral calcifications, convulsions, and mental retardation. Recently, a more variable clinical picture has been described, and the disease has been recognized with increasing frequency. Some studies have shown that a rather high percentage of the adult population have serologic evidence of infection, usually without associated clinical signs or symptoms. Two such surveys have been performed among children. Feldman and Sabin[7] used Toxoplasma egg antigen for intradermal testing and found no positive reactors in the 0- to 4-year age group, 5% in the 5- to 9-year age group, and 14% in the 10- to 19-year age group. At least 20 children were tested in each age range. The same authors reported no positive skin reactors and no positive titers among another group of normal children under 5 years of age.[8] MacDonald[9] did serologic tests on 100 children without finding a single positive reactor. He concluded that symptomless infections are not acquired in childhood.

RESULTS OF STUDY

As can be seen in Table 1, among 40 children tested in the 0- to 4-year age group there were 6 with serologic titers of 1:4 or higher, or an incidence of 15%. In the 5- to 9-year age group, 15 of 45, or 33%, of the subjects tested had similarly positive titers, and in the 10- to 15-year age group 6 of 17, or 35%, had positive titers. When titers for methylene-blue dye tests were plotted against patient age, no variation of test results with age could be demonstrated. A total of 41 of these children were also given skin tests. In the same age groups 7, 22, and 83% manifested dermal sensitivity.

5. Janku, J.: Pathogenesis and Pathologic Anatomy of Coloboma of the Macula Lutea in an Eye of Normal Dimensions and in a Microphthalmic Eye with Parasites in the Retina, Časop. lék. česk. **62**:1021, 1054, 1081, 1111, and 1138, 1923.

6. Wolf, A., and Cowen, D.: Granulomatous Encephalomyelitis Due to an Encephalitozoon (Encephalitozoic Encephalomyelitis): A New Protozoan Disease of Man, Bull. Neurol. Inst. New York **6**:306, 1937.

7. Feldman, H. A., and Sabin, A. B.: Skin Reactions to Toxoplasmic Antigen in People of Different Ages Without Known History of Infection, Pediatrics **4**:798, 1949.

8. Sabin, A. B., and Feldman, H. A.: Chorioretinopathy Associated with Other Evidence of Cerebral Damage in Childhood: Syndrome of Unknown Etiology Separable from Congenital Toxoplasmosis, J. Pediat. **35**:296, 1949.

9. MacDonald, A.: Incidence of Toxoplasma Infection in Northwest England: Transmission of Antibody from Mother to Infant, Lancet **2**:560, 1950.

Table 2 compares results of methylene-blue dye tests and of skin tests. It appears that a number of discrepancies exist.

All patients were studied with respect to the type and principal localization of the complaint or disease which had brought them to medical attention. The frequency with which positive serologic titers were encountered in various disease states was determined, and a careful search was made for possible signs of toxoplasmosis in each instance.

As is shown in Table 3, there were 25 patients with various diseases of the central nervous system. Of this number, 8, 32%, were found to have positive dye-

TABLE 1.—*Serologic and/or Skin-Test Evidence of Toxoplasmosis in Children of Various Age Groups, Expressed as Fractions of the Sample Tested*

Age Group, Yr.	Methylene-Blue Dye Test, Positive Results	Skin Test, Positive Results
0- 4	6/40	1/13
5- 9	15/45	5/22
10-15	6/17	5/ 6
Total	27/102	11/41

TABLE 2.—*Correlation of Skin Test with Methylene-Blue Dye Test*

Age Group, Yr.	Dye Test	Skin Test
0- 4	+ 2	+ 1
		− 1
	0 11	+ 0
		− 11
5- 9	+ 6	+ 3
		− 3
	0 16	+ 2
		− 14
10-15	+ 3	+ 2
		− 1
	0 3	+ 3
		− 0

test titers. The explanatory comments in Table 3 for Cases 7, 13, 14, 21, and 24 cannot be elaborated profitably. However, additional comments are necessary for Cases 8, 9, and 15.

CASE 8.—A. J. had many hospital admissions because of generalized convulsions. His birth and neonatal histories were not remarkable. No evidence of chorioretinitis was present, and roentgenograms of the skull revealed no intracranial calcification. The patient died during an attack of status epilepticus. An autopsy was performed, but pathological evidence of toxoplasmosis could not be found. His serologic titer was 1:4,096. It was not possible to check his mother's serum.

CASE 9.—W. C. was delivered spontaneously after a normal pregnancy. The neonatal period was uneventful. Development was retarded. At 4 years of age he began having periodic generalized convulsions. Pneumoencephalograms were interpreted as showing no abnormality; x-rays of the skull showed no abnormal calcifications, and repeated examinations of the fundi disclosed no evidence of chorioretinitis. The electroencephalogram was compatible with major

and minor convulsive disorders but did not show specific localization. He and both his parents had positive serologic titers for toxoplasmosis (patient 1:1,024; mother 1:64, and father 1:16).

CASE 15.—J. W. was delivered spontaneously after an uneventful pregnancy. At 3 months of age his head appeared to be enlarging more rapidly than normally, and he soon appeared definitely hydrocephalic. Development was severely retarded, and at one year of age he started

TABLE 3.—*Data in Cases of Various Diseases of the Nervous System*

Case	Age, Yr.	Color	Sex	Diagnosis	Dye-Test Titer	Skin Test	Convulsions	Psychomotor Retardation
1	1¼	W	F	Hydrocephalus	0	..	.....	+
2	1¼	N	M	Subdural hematoma	0	—	Focal	+
3	1 7/12	W	F	.....	0	..	.....	+
4	2	W	F	.....	0	—	.....	+
5	2	N	M	.....	0	..	Generalized	+
6	3	N	F	Encephalitis	0	—	.....	..
7	3½	W	F	.....	1:64	..	.....	+
8	4	N	M	Epilepsy	1:4,096	..	Generalized	..
9	4	W	M	Epilepsy	1:1,024	+	Generalized	+
10	4	N	M	Microcephalus, spastic quadriplegia	0	..	.....	..
11	4	N	F	Craniopharyngioma	0	—	.....	+
12	4	N	F	Epilepsy	0	..	Generalized	+
13	5	W	M	Epilepsy	1:64	+	Generalized	..
14	5	N	F	Epilepsy	1:16	..	Focal	..
15	6	W	M	Hydrocephalus	1:4	..	Generalized	+
16	6	W	M	Encephalitis	0	—	Generalized	..
17	6	N	F	Epilepsy	0	—	Focal	..
18	6	N	F	Epilepsy	0	..	Focal	..
19	7	W	F	Friedreich's ataxia	0	—	.....	..
20	7	N	M	Epilepsy	0	—	Generalized	..
21	7	N	M	Epilepsy	1:64	+	Focal	..
22	8	N	M	Epilepsy	0	—	Focal	..
23	9	N	M	.....	0	—	.....	+
24	9	N	M	Encephalitis	1:64	..	.....	..
25	11	N	M	Hydrocephalus; spastic paraplegia	0	..	.....	+

TABLE 4.—*Results in Patients with Chorioretinitis*

	Patient					Mother	
Patient	Race	Sex	Age, Yr.	Titer	Skin Test	Titer	Skin Test
J. W.	W	M	6	1:4	.....	1:64	.....
E. C.	W	F	8	0	30 mm.	1:64	50 mm.
W. W.	N	M	15	0	18 mm.	0	18 mm.

to have generalized major convulsions, which continued to occur at 4- to 6-month intervals. His weight was 18.5 kg.; his height, 110 cm.; his head circumference 69 cm., and his chest circumference, 60 cm. Evidences of healed chorioretinitis were seen. No intracranial calcifications could be demonstrated. Clinically, it was thought that he represented a case of congenital toxoplasmosis in spite of the titer of only 1:4. His mother's titer was 1:64.

Of these 25 patients with manifestations of central nervous system disorders, 2 had intracranial calcifications, but in neither were they associated with a positive skin test or serologic evidence of toxoplasmosis.

Three children with seemingly characteristic chorioretinopathy were encountered (Table 4); only one had a positive serologic test. This patient (same as Patient 15, Table 3) and one other were described as exhibiting bilateral healed chorioretinitis. The third child had acute chorioretinitis in the right fundus, but chronic chorioretinitis in the left. The last patient had had symptoms of visual disturbance for approximately six months and had been treated five years earlier on our service for meningococcal meningitis. His fundi were examined twice during that hospital admission, and each time they appeared normal. Both patients with chorioretinitis who had negative serologic tests had strongly positive skin tests. The mothers of all three children were asymptomatic and had no evidence of chorioretinitis, but either the skin tests or the serologic tests or both gave evidence of toxoplasmosis.

There were 13 patients who either had or recently had had evidence of pulmonary disease. Six of these had positive serologic tests, and five had titers of 1:64 or higher, although none had any other clinical features which could be definitely attributed to toxoplasmosis. Roentgenograms on none of the six revealed intracranial calcifications.

Four patients were being seen for hematologic disorders, including two with sickle-cell anemia and one each with lymphatic leukemia and thrombocytopenic purpura. Three of these had positive methylene-blue dye tests, but none exhibited any of the usual evidences of toxoplasmosis. The one who had essential thrombocytopenic purpura was subjected to splenectomy, but no pathological evidence of toxoplasmosis could be demonstrated microscopically in the surgical specimen.

Similarly, of nine patients with rheumatic fever, three had positive methylene-blue dye tests, but none had recognizable clinical evidence of toxoplasmosis. Sera from mothers of two of these three children also gave positive dye tests.

Six patients had various types of kidney disease. One of these, M. B., a Negro boy aged 6 years, had a positive test (titer, 1:64). He had no clinical evidence which could be attributed to toxoplasmosis, and his mother's serologic test was negative.

Eight patients had generalized lymphadenopathy; four of these also had enlargement of the liver and spleen. Of the eight, two had positive dye tests. One, C. H., a Negro girl aged 3 years, had a serologic titer of 1:64 but a negative skin test. She had general glandular enlargement, together with moderate enlargement of the liver and spleen, for which no adequate explanation was ever found. Her mother's dye-test titer was also reported as 1:64. The other patient, R. A., a white boy 11 years of age, had a positive titer of 1:256. He had been hospitalized for a fever of undetermined origin with associated lymphadenopathy.

Of the remaining 18 patients, representing various miscellaneous diseases, 3 had positive dye tests. The first, A. M., a Negro girl aged 5 years, was admitted to the hospital because of cellulitis of the leg. There had been no previous illness except measles and chicken pox. Her dye-test titer was 1:64, but serum from the mother gave a negative reaction. The second patient, E. J., a Negro girl aged 7 years, was admitted with a fever of undetermined origin (temperature 106 F.), cervical lymphadenitis, and a diffuse erythematous maculopapular rash located on the chest, abdomen, and back. The cause of the disease was not determined by clinical and laboratory examinations. She and her mother had serum antibody titers

of 1:4. The third patient, S. M. B., an 11-year-old Negro girl, was admitted for suspected rat-bite fever. She had a generalized macular rash, but the physical findings were otherwise not remarkable. The dye-test titer was 1:256, and the skin test was positive.

COMMENT

Evaluation of the data collected in this study is difficult. If we assume accuracy and specificity for the methylene-blue dye test, a viewpoint which appears to be warranted, it follows that infection with Toxoplasma is more frequent than was previously suspected, and also that infection of sufficient severity to result in serologic effect has occurred without production of recognizable clinical disease or its residua. The height of the dye-test titer in a majority of the children probably is best explained by recent, and hence postnatal, infection, since in studies on congenital toxoplasmosis and the mothers giving birth to children with this disease it has been shown that titers gradually decline over a period of four or more years. However, the possibility also exists that congenital transmission of toxoplasmosis had occurred, but that the infection had remained latent until a precipitating event of undetermined character allowed it to become manifest.

Again, assuming that the methylene-blue dye test yields neither false-positive nor false-negative results, validity of the skin test (mouse antigen) must be questioned. False-negative skin tests in the face of positive dye tests are known to occur occasionally. They were encountered six times in our experience. Positive skin tests in the absence of positive dye-test titers are extremely rare. Using egg antigen for skin testing, Feldman has never encountered a positive result if the reaction to the dye test was negative.[10] It is therefore of considerable interest that five such instances were recorded when mouse antigen was used. Two of these subjects were of the same family.

Retrospective analysis of clinical records was augmented whenever possible by recalling patients to the hospital for repeat examinations and additional history. However, with the diagnosis of toxoplasmosis being based either on a combination of typical physical and laboratory findings or on the finding at biopsy or at autopsy of Toxoplasma organisms in tissue, it is usually impossible to exclude the diagnosis in a living patient. This difficulty is particularly pertinent in relation to the eight patients who had disease of the central nervous system and positive dye tests. With respect to other arbitrary categories of disease into which the entire group was divided, no cardinal signs, symptoms, or historical facts were discovered which would have served as a reasonable basis for relating the presenting disease with toxoplasmosis.

SUMMARY AND CONCLUSIONS

A total of 102 infants and children at the Charity Hospital of Louisiana were examined for the Toxoplasma antibody, the methylene-blue dye test being used. The incidence of titers in excess of 1:4 in various age groups was as follows: 0 to 4 years, 15%; 5 to 9 years, 33.5%, and 10 to 15 years, 35%. A total of 41 patients had skin tests with an antigen made from mouse peritoneal exudate. For the three age groups, positive results were obtained, respectively, in 7.6, 22.7, and 83.3%.

10. Feldman: Personal communication to the authors.

Five patients who had negative dye tests had positive skin tests. Attempted correlations of the disease which brought the patient to medical attention and laboratory evidences of toxoplasmosis are discussed. A presumptive relation was suspected in a few instances. However, a majority of the children with either significantly high titers or positive skin tests had no recognizable clinical manifestations of toxoplasmosis.

The data suggest either that there is an asymptomatic form of the disease in children, whether infection is acquired congenitally or postnatally, or that the antibodies measured by the methylene-blue dye test are not highly specific. The first possibility is favored.

The demonstration of the Toxoplasma antibody and/or a positive test for dermal sensitivity to mouse antigen in children suspected of having the disease should be considered of limited diagnostic value, since 25% of randomly chosen subjects have positive dye tests and since a disturbing lack of correlation between the two tests exists.

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Dr. H. A. Feldman performed the methylene-blue dye tests.

LIPID NEPHROSIS IN CHILDREN

Observations Over a Period of Twenty-Six Years

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IN A PREVIOUS communication [1] we reported our observations on children with the nephrotic syndrome over a 20-year period. We wish now to report on observations for over six additional years of some of these patients. We shall also report on additional patients seen subsequently.

MATERIAL

The material consists of the following: (1) patients who died while under observation and (2) patients now alive followed for a period of 4 years to 26 years. All these patients were seen by one of us (J. L. K.) at the Mount Sinai Hospital at frequent intervals during the entire period.

All patients on admission gave a history of an insidious onset of illness and generalized recurrent edema. They had a normal or slightly elevated blood pressure, massive albuminuria, normal or moderately increased blood urea content, a high serum lipid level, and a low serum protein concentration.

We shall first discuss the patients seen before the introduction of sulfonamides and antibiotics in the treatment of infections. We shall then compare their course of illness with that of those seen after the introduction of these new drugs. We shall not at this time include any children who were treated with corticotropin (ACTH) or cortisone acetate.

We have classified those living as follows: (1) clinically well, (2) clinically well but with albuminuria or hypertension or both, and (3) in poor condition when last seen, with symptoms of chronic progressive glomerular nephritis. Most of the children in the last class had azotemia, hypertension, eyeground changes, or evidence of cardiac involvement.

We shall also discuss the postmortem material before and after the use of chemotherapy. Necropsies were made on 21 patients; of these, 13 were in the first group and 8 in the second group.

A total of 57 children will be discussed, of whom 33 were seen before the use of chemotherapy. As can be seen from Table 1, in the older group five have recovered, six were clinically well but had albuminuria, and the condition of one of the patients when last seen was poor. The remainder have died. In the more recent group, of 24 patients, 3 have recovered, 4 were clinically well but had albuminuria or hypertension, and 2 were in poor condition. The remainder had died. It is noted that the ultimate mortality in the two groups was about the same.

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1. Schwarz, H.; Kohn, J. L., and Wiener, S. B.: Lipid Nephrosis: Observations over a Period of 20 Years, Am. J. Dis. Child. **65**:355 (March) 1943.

PATIENTS FIRST OBSERVED AND FOLLOWED BEFORE INTRODUCTION OF CHEMOTHERAPY

We shall first report on 12 patients who have been followed from 10 to 26 years. They have been followed 26, 25, 24, 23, 17, 17, 16, 16, 12, 10, 10, and 10 years, respectively. With one exception all these patients, we have reason to believe, are in good health and leading normal lives. The one exception is a child who when last seen had symptoms of chronic progressive glomerulonephritis. Of the remainder, seven had albuminuria and two also had hypertension. It was noted that the duration of the edematous manifestations was from 5 to 12 months in eight patients and from 18 months to 8 years in the other four (Table 2).

We wish to present the summary of the histories of four of these patients. A different course of the illness is noted in each of these.

CASE 1.—B. D. W. was followed for 26 years. She was 8 years old when symptoms were first observed. During the first year of illness, her course was typical, with many episodes of recurrent infections, recurrent edema, and diuresis. After this period there was improvement in her general condition, and her blood urea nitrogen was within normal limits. During

TABLE 1.—*Total Lipid Nephrosis Patients Observed over Period of Twenty-Six Years and Status at Conclusion of Study*

Group *	Total No. of Patients	Clinically Well		Condition Poor	Deceased
		Without Albuminuria	With Albuminuria		
1	38	5	6	1	21
2	24	3	4	2	15

* Group 1 consists of patients seen first before introduction of chemotherapy. Group 2, of patients seen first after the introduction of chemotherapy.

the next year the albuminuria became less. At the age of 20 she married and was subsequently delivered of two normal children. However, during the last four months of both pregnancies toxemia, characterized by hypertension, albuminuria, and moderate blood nonprotein nitrogen retention, developed. Upon termination of these pregnancies, her urine and blood chemical values returned to normal.

When 31 years old, she was found to have diabetes mellitus. The following year she again became pregnant. During the early part of her pregnancy, diabetic ketosis developed. Six weeks prior to term, she was delivered of a large, edematous baby, which died soon after birth. During the latter pregnancy there was a moderate increase in blood pressure. There was no blood urea nitrogen retention or albuminuria. She is now living a normal life. Recent function tests showed evidence of kidney impairment.

CASE 2.—J. K. was admitted to the hospital 25 years ago, at the age of 2½ years. During a long hospital stay, his illness followed the usual clinical course. He improved after measles infection. His albuminuria persisted, with a moderate hypertension. When he was 14 years old, kidney function tests were normal and an Addis count revealed an abnormal amount of formed elements. He was rejected for military service during World War II on three different occasions. He was able to carry on his work as a salesman. At present he has moderate hypertension and albuminuria but is in excellent health. We can assume that this patient has adequate kidney function.

CASE 3.—Y. S. was first seen when 4 years old. The nephrosis followed the usual clinical course. The patient had measles two years after the onset of nephrotic symptoms without any apparent effect on the course of the illness. When she was last seen, more than 17 years after onset, albuminuria was still present, with a high grade of hypertension. Her

heart was enlarged. Funduscopic examination revealed narrowed retinal vessels. Blood urea nitrogen was normal. It was our impression, however, that she had progressive kidney involvement. We have been unable to locate her for the past five years.

CASE 4.—N. D. was first seen when he was 2½ years old and was followed for 17 years. During the first two years of illness, he contracted infection with Diplococcus pneumoniae Type 6 on six different occasions. During this period he had measles and exhibited some

TABLE 2.—*Data on Patients Seen Before Introduction of Chemotherapy and Condition When Last Seen**

Patient	Sex	Age at Onset, Yr.	Follow-Up, Yr.	Condition When Last Seen			Total Duration of Nephrotic Symptoms, Mo.	Comment
				Year	Blood Pressure	Albumin in Urine		
I. S.	M	2½	26	1951	120/75	—	6	Clinically well; in military service 2 yr.
J. K.	M	2	25	1949	150/80	Trace	5	Clinically well; rejected for military service several times; probably has chronic nephritis; blood chemical values normal
B. D.	F	8	24	1952	108/82	Trace	10	During 2 pregnancies mild toxemia developed with hypertension and albuminuria; in 1947 diabetes developed during 3d pregnancy; no hypertension seen in diabetic ketosis; kidney function tests show 60% of normal
R. P.	F	4	23	1950	120/80	—	10	Clinically well
Y. S.	F	4	17	1946	155/95	Trace	24	Probably died; when last seen had an enlarged heart; eyeground changes as seen in chronic nephritis
N. D.	M	2	17	1950	110/64	Trace	18	Clinically well; during nephrotic stage had a bacteremia with D. pneumoniae Type 6 on 4 separate admissions; when last seen, urine phenolsulfonphthalein excretion was normal; blood chemical values were normal
M. A.	F	1½	16	1941	110/70	—	6	Clinically well; not seen since 1941 but informed she is well
J. G.	M	2	16	1951	120/70	Trace	23	Clinically well since discharge
J. S.	M	3	12	1942	100/65	—	23	Clinically well since discharge; in hospital for 1 yr. after onset; informed in 1951 that child clinically well thereafter
B. B.	F	3	10	1951	100/70	Trace	12	Clinically well; azotemia and hypertension for 4 mo. during early course of illness; dramatic improvement following an abdominal paracentesis
S. S.	M	4	10	1951	102/70	—	9	Clinically well; no azotemia at any time
M. K.	F	6	10	1951	110/70	Trace	26	Clinically well; had low-grade azotemia during 3 hospital admissions; blood urea nitrogen was 22 to 26 mg.; urine showed an occasional red blood cell for 4 yr. after first admission

* Children followed from 10 to 26 years.

improvement for about two months. There were no clinical symptoms of kidney involvement two years after onset. The patient has developed normally, without hypertension and albuminuria.

PATIENTS FIRST OBSERVED AND FOLLOWED AFTER INTRODUCTION OF CHEMOTHERAPY

Since the introduction of sulfonamides and antibiotics, nine children who were admitted with a nephrotic syndrome have been followed from four to eight years. Three of these have apparently made a complete recovery; four others are clinically

well but have albuminuria. The two others when last seen had evidence of chronic progressive glomerulonephritis (Table 3). In the children who are clinically well, the edema was present for 6 months, 8 months, 10 months, 12 months, 14 months, 20 months, and 7 years.

We wish to present summaries of the histories of two children who were edematous for longer periods. Both of these children had measles during the course of illness. One child remained clinically well for eight months before the return of symptoms; the other made a complete recovery.

TABLE 3.—*Data on Patients Seen After Introduction of Chemotherapy and Condition When Last Seen*

Patient	Sex	Age at Onset, Yr.	Follow-Up, Yr.	Condition When Last Seen			Total Duration of Nephrotic Symptoms, Mo.	Comment
				Year	Blood Pressure	Albumin in Urine		
R. J.	M	3	8	1951	110/70	2+	84	Azotemia for 5 mo. during hospital stay; edema intermittently for 6 yr.; during one edematous stage had measles followed by disappearance of edema and no albuminuria for 7 mo.; for last year no edema present; albumin 2+; blood chemical values normal
P. L.	M	4½	7	1951	110/60	—	10	Well since discharge; no azotemia or hypertension
C. O.	M	2½	6+	1951	100/70	Trace	8	Clinically well; occasional azotemia and hypertension during first 5 mo. of illness
C. S.	F	5	6	1948	100/70	—	6	Clinically well; informed in 1952 that blood pressure and urine were normal
L. K.	M	3	5	1951	100/65	—	20	Edema and albuminuria cleared after measles; no azotemia; had D. pneumoniae bacteremia during one infectious episode
D. S.	M	1	4	1951	100/75	1+	12	Clinically well; blood chemical examination is normal at present
J. W.	F	4½	4	1951	96/60	1+	14	Clearing of edema after measles; azotemia on only one examination; clinically well
R. G.	F	3	4	1951	110/..?	2+	3	Child is in poor condition at present; at onset no azotemia or hypertension; moderate azotemia 1 yr. after onset; abdominal paracenteses done 20 times
N. P.	F	5	4	1945	155/105	2	3½	Child in poor condition when last seen; had measles 10 mo. after onset with clinical improvement but return of symptoms after several wk.; four yr. after onset, had symptoms of tetany, azotemia, hypertension, and evidence of poor kidney function

CASE 5.—L. K. first had symptoms of nephrotic syndrome when 2 years old. Over a period of 17 months, there were eight hospital admissions. He had frequent severe respiratory infections and on one occasion had a blood culture positive for D. pneumoniae. These infections were controlled with the use of sulfanilamide and penicillin. During the last admission he had measles, which was followed by diuresis and with apparent recovery. Although he had had many severe respiratory infections prior to measles, only once had there been resultant diuresis. It should be noted that he had no nonprotein nitrogen retention during his entire illness. His blood pressure had been increased occasionally.

CASE 6.—R. S. was observed for eight years. He had recurrent edema for over two years, when he became infected with measles. He was well for six months until an appendectomy, after which all symptoms returned. For the next five years there was recurrent edema, but within the last year, except for albuminuria, he has been clinically well.

PATIENTS WHO DIED BEFORE INTRODUCTION OF CHEMOTHERAPY

There were 21 children who died during the period before the introduction of chemotherapy. Of this group, 16 died in less than one year after the onset of illness, and 12 of these 16 died in less than six months after onset (Table 4). Nineteen died of a bacterial complication, the most frequent presenting symptom being peritonitis with a concomitant bacteremia. In only two of the entire group could death be attributed to poor kidney function. It is conceivable, of course, that if secondary infection had not intervened there might have been a resultant chronic nephritis.

Thirteen necropsy examinations were made. Minimal glomerular changes, with one exception, were found in 10 patients who died within one year of onset of nephrotic symptoms. Only a careful search revealed a rare thickening of the glomerular capsule and adhesion of some of the tufts to the capsule.

In the three patients who died after one year of illness, examination of the kidney showed some fibrotic glomeruli with scarring, but even these changes were not very extensive.

PATIENTS WHO DIED AFTER INTRODUCTION OF CHEMOTHERAPY

Fifteen children died after the introduction of chemotherapy (Table 5). Only five died during the first year. One of the latter group may have died as the result of an acute glomerular nephritis. One child died of an intercurrent infection outside the hospital. We believe the life of the other three could have been prolonged if better judgment in treatment had been applied.

One of these children collapsed after intense diuresis following parathyroid hormone injections. There was evidence of extreme electrolyte loss. We felt that appropriate treatment had been delayed.

A second child died during the course of severe diarrhea. Again there was an extreme electrolyte loss with delay of appropriate treatment.

A third child had a very large peritoneal effusion with symptoms of pressure in the pleural cavities. An abdominal paracentesis was delayed because of a severe skin infection over the abdomen. As shown at necropsy, bilateral pleural drainage should have been instituted and an abdominal paracentesis done.

Eight necropsy examinations were made. Two were done from five to seven months after onset of illness. In both instances there were minimal changes in glomeruli. The others, who died 18 months, 18 months, 2 years, 3½ years, 3 years, and 3 years after onset, all showed evidence of chronic glomerulonephritis.

TREATMENT

The rationale of treatment of a patient with lipid nephrosis depends perhaps on the concept as to whether the syndrome is of extrarenal origin, purely renal, or a combination of the two. But, regardless of the concept, the first object of treatment when the patient is first seen is to induce diuresis, especially when the edema is extreme. It is hoped that such induced diuresis will retard or arrest the disease process. Litchfield, Norton, Moss, and Greenblatt [2] have recently attempted to evaluate various methods of treatment. We shall discuss briefly some of these

2. Litchfield, H. R.; Norton, R.; Moss, A. H., and Greenblatt, I. J.: Evaluation of Serum Albumin, Potassium and Sodium Salts and Other Methods of Treatment in Nephrosis, Am. Pract. & Digest. Treat. **1**:1050 (Oct.) 1950.

TABLE 4.—*Data on Patients Who Died During Course of Lipid Nephrosis Before Introduction of Chemotherapy*

Patient	Age at Onset, Yr.	Length of Illness, Mo.	Laboratory Data and Comment	Cause of Death	Necropsy
F. K.	7	1½	Blood urea nitrogen 12 to 30 mg. per 100 cc.; urine contained albumin (3+) and moderate casts; phenolsulfonphthalein excretion 38%; blood pressure 130/90 to 135/105	Unknown; had two episodes of stupor at home; pneumonia	None
E. M.	4	5	No azotemia or hypertension; urine contained albumin (3+) and a few casts	Pneumonia	None
B. F.	11	4	No azotemia or hypertension; urine contained albumin (3+) and many granular casts; phenolsulfonphthalein excretion 25 and 32%	Pneumonia; pneumococcic peritonitis	None
E. W.	5	9	Blood urea nitrogen 12 to 25 mg.; no hypertension; urine contained albumin (3+) and many granular casts	Diphtheria; said to have been clinically well before onset of diphtheria	None
M. A.	1½	7	Persistent azotemia for 3½ mo.; no hypertension; urine contained albumin (3+) and many casts	Unknown; had operation for decapsulation of kidneys	None
B. R.	7	2	No azotemia or hypertension; urine contained albumin (3+) and many casts	D. pneumoniae Type 1; peritonitis	None
A. P.	2½	4	No azotemia or hypertension; urine contained albumin (2+), casts (2+), and occasional red blood cells	D. pneumoniae peritonitis; meningitis	Glomerulae normal and tubular swelling
A. Z.	2	3	Slowly rising blood urea nitrogen (10 to 24 to 32 mg. per 100 cc.); urine contained albumin (4+) and occasional cast	Peritonitis	None
R. S.	2½	1½	No azotemia; urine contained albumin (3+) and a few granular casts	Streptococcus bacteremia; peritonitis	Kidney large; interstitial intracellular infiltration; glomerulae normal with tubular swelling
M. F.	2¼	20	Blood urea nitrogen was 22 to 14 mg.; no hypertension; urine contained albumin (3+) and casts (2+); phenolsulfonphthalein excretion 48%	Blood culture, D. pneumoniae Type 2; ascitic fluid, hemolytic Streptococcus	None

H. S.	2	¼*	No azotemia; urine contained albumin (3+) and casts (2+)	D. pneumoniae Type 4; peritonitis	Glomerulae normal
M. L.	4	36	No azotemia; no hypertension; urine contained albumin (3+) and many casts and red blood cells; phenolsulfonphthalein exeretion 35 to 45%	Bacteremia (D. pneumoniae Type 4 and Streptococcus)	Chronic glomerulonephritis
S. M.	8	36	No significant azotemia or hypertension; urine contained albumin (3+), few casts, and red blood cells	Peritonitis; blood culture positive for D. pneumoniae Type 4	Chronic glomerulonephritis but many glomerulae normal
B. H.	2	12	Blood urea nitrogen was 27 mg. (single determination)	Peritonitis	None
S. T.	2½	4	No azotemia or hypertension; urine contained albumin (3+) and a few red blood cells	Type 4 D. pneumoniae bacteremia and peritonitis	Glomerulae normal
J. P.	2	1½	No azotemia or hypertension; urine contained albumin (2+); cholesterol normal	Blood culture positive for D. pneumoniae and a viridans Streptococcus	Glomerulae normal
M. D.	5	3	No azotemia or hypertension; urine contained albumin (4+) and a few casts	D. pneumoniae peritonitis	Glomerulae normal; atheroma in aorta
M. S.	4	2	No azotemia or hypertension; urine contained albumin (4+) and 1 to 2 red blood cells	D. pneumoniae peritonitis	Rare glomerulus with fixed loops; calcium deposits in tubules; interstitial pancreatitis; hydroureter with hydronephrosis of lower pole of left kidney
M. K.	2½	5	No significant azotemia except for blood urea nitrogen of 38 mg. prior to death; no hypertension	Type 4 D. pneumoniae bacteremia and peritonitis	Occasional glomerulus seen with fused loops
G. W.	3	24	No hypertension; had azotemia for greater part of course; urine contained albumin (3+), few casts, and red blood cells; free of edema for 1 yr. then recurrence 6 wk. prior to death	Type 23 D. pneumoniae	Chronic nephritis with few fibrotic glomerulae; many plump tufts and adhesions of loops to capsule
R. H.	3	12	No azotemia or hypertension; urine contained albumin (4+) and occasional red blood cell and cast	D. pneumoniae Type 23 bacteremia and peritonitis	Moderate glomerular changes; scattered thickening of glomerular tufts; proliferative changes sporadic

* The patient died in one week.

TABLE 5.—*Data on Patients Who Died During Course of Lipid Nephrosis After Introduction of Chemotherapy*

Patient	Age at Onset, Yr.	Follow-Up, Mo.	Duration of Edema, Mo.	Laboratory Data and Comment	Cause of Death	Necropsy
N. M.	1½	7	7	In another hospital for 6 mo. with edema; given sodium and potassium salts; no azotemia; moderate hypertension; high cholesterol; urine contained moderate number of red blood cells and casts	Died suddenly while receiving sodium and potassium salts; at time of death erysipeloid eruption over abdomen	Lung edematous; 300 cc. of fluid in both pleural cavities, 1,700 cc. in abdominal cavity; kidney showed a few hyaline glomerulae with adhesions to capsule
M. N.	1	5	5	Given sodium and potassium salts; edematous during entire period of observation; no azotemia; no hypertension; urine contained a few red blood cells and casts	Severe diarrhea with dehydration and ketosis	Kidneys showed a rare glomerular swelling with adhesion to capsule
K. W.	2	36	24	Moderate azotemia with moderate hypertension; recurrent edema for 2 yr.; measles gave only a temporary remission; no effect from high doses of sodium and potassium salts	Progressive nephritis	None
I. F.	4½	48	18	Azotemia present early after onset; progressive hypertension; free of edema for several mo. before death	Progressive nephritis	None
R. P.	2¼	36	24	Low-grade azotemia; moderate hypertension; edema-free for 1 yr. before death	Progressive nephritis and purulent peritonitis	Diffuse chronic glomerular nephritis; generalized atherosclerosis and peritonitis
A. K.	5	36	24	Progressive azotemia and hypertension after 6 mo. of illness; edema-free for 1 yr. before death	Progressive chronic nephritis; terminal pericarditis	Diffuse chronic glomerular nephritis; kidney showed extensive fibrosis with round cell infiltration; atherosclerosis of aorta; myocarditis and pericarditis
E. N.	1⅝	18	18	Progressively increasing azotemia; last blood urea nitrogen determination 114 mg.; no hypertension; cholesterol 1,720 mg.; edema from onset to death; urine contained albumin (4+), casts, and red blood cells throughout course; given sulfonamides, penicillin, and blood	Died one day after 4th admission; uremia, cardiac decompensation; bronchopneumonia	Diffuse chronic glomerulonephritis
J. N.	5	18	18	Low-grade azotemia during first admission; blood urea nitrogen 10 to 25 mg.; urine contained albumin (2 to 3+), many granular casts, and occasional red blood cells; 1 yr. later progressive azotemia; blood urea nitrogen was 250 mg. and hypertension (190/140); urine contained albumin, (1 to 2+) and occasional cast; extreme generalized edema during first admission, then free of edema for 1 yr.; slight edema of face on last admission; digitalis on last admission	Uremia; cardiac failure	Diffuse chronic glomerulonephritis with atrophy of tubules; interstitial fibrosis with round cell infiltration

S. S.	4	24	12	Moderate generalized edema on first admission without azotemia or hypertension; cholesterol 1,080 mg.; total protein was 3.5 gm.; urine contained albumin (4+), occasional cast, and red blood cell; given blood and plasma with diuresis; edema-free 1 yr.; then progressive increase in edema; moderate hypertension (118/86 to 140/114); progressive rise in blood urea nitrogen to 240 mg.; cholesterol 1,250 mg.; urine contained albumin (4+), many granular casts, and red blood cells	Uremia	Diffuse chronic glomerulonephritis
S. S.	1⅚	26	20	Azotemia for 5 mo. during latter part of first admission; blood urea nitrogen 12 to 64 mg., and then elevated up to 72 mg. during remainder of course; mild hypertension at onset and intermittently during course; urine contained albumin (2 to 4+), moderate casts, 4 to 10 red blood cells; no edema for latter part of course	Cardiac failure; bronchopneumonia	None
J. H.	3	1*	4	No azotemia or hypertension except on day of admission; blood urea nitrogen was 28 mg.; blood pressure 120/90; urine contained albumin (2 to 3+), and occasional red blood cell, and cast	Unknown	None
G. R.	1⅓	3	6	Insidious onset; azotemia and hypertension throughout course; blood urea nitrogen up to 59 mg.; cholesterol 1,120 mg.; blood pressure 120/80 to 170/120; urine contained albumin (4+), and few red blood cells; edema throughout	Three mo. after discharge patient was brought back to hospital; dead on arrival	None
F. C.	2	3†	3	Azotemia and hypertension during latter part of illness; edema throughout; cholesterol 1,080 mg.; urine contained albumin (2 to 4+), granular casts, and red blood cells	Given antuitrin®-growth as diuretic; had profuse diuresis; lost 13 lb. in 2 days; went into shock and died	None
K. B.	3½	42	12	Edema-free for last 2½ yr.; azotemia for 3 yr. of illness; hypertension since onset; cholesterol 920 to 3,440 mg.; urine contained albumin (4+), granular casts, and red blood cells	Progressive renal failure (uremia)	Diffuse glomerular fibrosis with atrophy of tubules
C. S.	1⅝12	33	9	No significant azotemia; blood urea nitrogen values 12 to 22 mg. with one of 37 mg.; hypertension from onset; cholesterol 480 to 1,600 mg.; urine contained albumin (3+), many casts, and red blood cells; no edema for last 2 yr. (?) or hypertension (?)	Died suddenly during paracentesis	None

* The patient died one month after discharge.
† The patient died three months after onset.

methods, with the exclusion of the use of corticotropin (ACTH) and cortisone. We shall limit ourselves to consideration of those children who had little or no azotemia when first seen.

Advocates of one form of treatment or another state that treatment is likely to be more effective if given early in the disease. This has not always been our experience. We believe that in many cases it is not possible to make a definite diagnosis of lipid nephrosis for several months after onset of symptoms.

In most instances a high protein diet was given to compensate for the great loss of protein in the urine. The maximum amount of protein in the diet was about 3 gm. per kilogram of body weight.

The prescribed diet was usually low in sodium, in chlorides, and sometimes in fat. In contrast, some advocate the inclusion of large amounts of sodium and potassium by mouth in the form of acetate or lactate. Fox and McCune [3] felt that the correction of the low plasma sodium and bicarbonate might move the water out of the intracellular components of the body. The treatment was modified when the plasma sodium became stabilized at normal level. At first these patients became more edematous, the edema being followed not infrequently by a diuresis. After such diuresis smaller amounts of the salts were continued in order to maintain a normal electrolyte balance and a protracted remission. In our experience this treatment has proved to be unsatisfactory in most instances. Some of the disadvantages were that the child became very thirsty, vomited frequently, was anorectic, and in some instances became very lethargic. Symptoms of severe alkalosis had to be watched for. It was necessary to do frequent chemical examinations of the blood for carbon dioxide, chloride, sodium, and potassium.

Another method was the giving of large amounts of concentrated low salt serum albumin intravenously over varying periods of time. In our experience, in about half of the patients a diuresis was obtained. However, in most instances the edema soon returned. Presumably the increased plasma albumin concentration increased the blood volume, with a resultant increase in renal blood flow with fluid and salt loss. At the present time this method of treatment is very costly. Before the concentrated albumin was available, we had tried giving frequent serum transfusions with no effect. In several children we used serum from patients who had apparently recovered from lipid nephrosis.

At times various endocrines have been given by us, particularly thyroid, thyroxin, parathyroid, and antuitrin®-growth. At other times we used large amounts of vitamins, particularly the B complex and vitamin A. We never obtained consistently satisfactory responses.

With the exception of mercury, none of the diuretics have been of value. Because of severe reactions, sometimes fatal, following the use of mercury we have not employed it in recent years.

An acute infection during the course of the nephrotic syndrome was often followed by diuresis and sometimes with an apparent arrest of the disease process.

3. Fox, C. L., Jr., and McCune, D. J.: Electrolyte Changes in Nephrosis: Occurrence of Diuresis Following Administration of Sodium and Potassium Salts, Am. J. M. Sc. **216:1** (July) 1948.

Infection with measles seems to be of particular value. Meizlik and Carpenter,[4] Barnes, Moll, and Janeway,[5] Hutchins and Janeway,[6] Blumberg and Cassady,[7] and Rosenblum, Lander, and Fisher[8] have recently discussed this subject. We have seen diuresis follow measles in almost every instance. In several children we have had prolonged improvement or recovery even with a history of two years of illness. In one child there was an apparent recovery for a period of six months, followed by a recurrence of the syndrome concomitant with acute appendicitis.

Abdominal paracentesis should be done whenever there is evidence of pulmonary embarrassment. Frequently there is drainage from the abdominal drainage site for a prolonged period, with complete disappearance of the edematous phase.

Several children suddenly lapsed into a state of collapse during or after a diuresis, diarrhea, or abdominal paracentesis. It was of great importance to be on the alert for excessive fluid loss. Appropriate treatment for such excessive loss of fluid and electrolytes had to be instituted promptly.

COMMENT

It is not our intention to go into an exhaustive discussion of the possible etiological factors which might clarify our conception as to the etiology and course of lipid nephrosis. This has been done recently by Bradley and Tyson,[9] Block, Jackson, Stearns, and Butsch,[10] Heyman and Alperin,[11] Barnes, Moll, and Janeway,[5] Rennie,[12] Seegal and Wertheim,[13] and Barnet, Forman, and Lauson.[14]

Klemperer,[15] pathologist to the Mount Sinai Hospital, has examined all our necropsy material. It would be of interest to review his comments at various periods after the onset of illness.

First, of a child who died of an intercurrent infection five months after onset of nephrotic symptoms, he stated that "glomerular lesions seen in this child after a

4. Meizlik, E. H., and Carpenter, A. M.: Beneficial Effect of Measles on Nephrosis: Report of 3 Cases, Am. J. Dis. Child. **76**:83 (July) 1948.

5. Barnes, L. A.; Moll, G. H., and Janeway, C. A.: Nephrotic Syndrome: Natural History of the Disease, Pediatrics **5**:486 (March) 1950.

6. Hutchins, G., and Janeway, C. A.: Observations on the Relationship of Measles and Remissions in the Nephrotic Syndrome, Am. J. Dis. Child. **73**:242 (Feb.) 1947.

7. Blumberg, R. W., and Cassady, H. A.: Effect of Measles on the Nephrotic Syndrome, Am. J. Dis. Child. **73**:151 (Feb.) 1947.

8. Rosenblum, A. H.; Lander, H. B., and Fisher, R. M.: Measles in the Nephrotic Syndrome, J. Pediat. **35**:574 (Nov.) 1949.

9. Bradley, S. E., and Tyson, C. J.: "The Nephrotic Syndrome," New England J. Med. **238**:223 (Feb. 12) 1948; 260 (Feb. 19) 1948.

10. Block, W. M.; Jackson, R. L.; Stearns, G., and Butsch, M. P.: Lipid Nephrosis: Clinical and Biochemical Studies of 40 Children with 10 Necropsies, Pediatrics **1**:733 (June) 1948.

11. Heyman, W., and Alperin, L. J.: Lipemic Nephrosis With and Without Nephritis, Am. Pract. **3**:680 (July) 1949.

12. Rennie, J. B.: The Oedematous Syndrome of Nephritis with Special Reference to Prognosis, Quart. J. Med. **16**:21 (Jan.) 1947.

13. Seegal, D., and Wertheim, A. R.: Recent Advances in Our Knowledge Concerning the Nephrotic Syndrome, Bull. New York Acad. Med. **25**:605 (Oct.) 1949.

14. Barnet, H. L.; Forman, C. W., and Lauson, H. D., in Advances in Pediatrics, Chicago, Year Book Publishers, Inc., 1952, Vol. 5, p. 53.

15. Klemperer, P.: Personal communication to the authors.

short course of illness, even though sparse, are the residual of a preceding inflammatory process which has left the kidney more permeable to albumin."

Second, of a child who had been ill for a year and died during peritonitis with bacteremia, he stated:

> This patient had the clinical features of a lipid nephrosis. Therefore, the glomerular changes must be interpreted more rigidly. There is a thickening of the glomerular tuft in a number of glomeruli, which points to some degenerative process in the basement membrane. The occasional loop adhesions and the plumpness of the tufts are features which may be seen in the course of chronic glomerulonephritis. While proliferative phenomena of the glomeruli are only sporadic, their presence cannot be neglected. This case can not be accepted as a case which fullfills the criteria of a true lipid nephrosis. One is more inclined to interpret the renal changes as a residue of a preceding inflammatory process which left the kidney parenchyma more permeable to albumin. The tubular epithelium shows the usual changes, and only a moderate amount of fat is seen.

His comments on a child who had been ill for two years with moderate azotemia and died during peritonitis were as follows:

> The correct interpretation of this patient is possible only by correlating the clinical features with the anatomic features. The kidney showed multiple scars including many fibrotic glomeruli and atrophied tubules, wide areas of strikingly dilated tubules with flattened epithelium, and convoluted tubules filled with albumin and vacuolated, the vacuoles being due not only to infiltration with double refractile fat but also to a severe degenerative process. The majority of the glomeruli do not show striking changes on superficial examination except for the presence of albumin in the capsular spaces. On close examination, however, one finds adhesions, loops, and plump tufts. By correlating the facts with the histological picture, one comes to the conclusion that the child had a glomerulonephritis which left definite scars but also left the glomeruli in an altered condition, permitting the passage of albumin, so that the constant loss of albumin is a factor in the clinical picture.

To summarize, there was sparse glomerular involvement in the patient after five months' illness, moderate after one year, and extensive involvement after two years.

Klemperer [15] believed the glomerular lesion at any period after onset was inflammatory in origin. He suggested, however, that the early changes were not those seen in an acute hemorrhagic glomerular nephritis during or following a hemolytic Streptococcus infection.

If one concedes that lipid nephrosis is primarily a kidney disease, does improvement or recovery following measles or other infection mean that there has been an arrest or reversal of kidney pathology? We have seen an apparent recovery following measles two or more years after the onset of illness, when presumably there had been extensive kidney damage. On the other hand, we have reported one patient who had apparently recovered. Some years later during the course of two pregnancies, there was evidence of kidney inadequacy.

After our prolonged period of clinical observation, we were not entirely convinced that lipid nephrosis was primarily a kidney disease. Perhaps there was some inciting extrarenal factor which acted directly on the glomeruli and tubules to cause dysfunction of protein absorption. Certainly, pathologically we saw little damage to the glomeruli in children who died within six months after onset. But can one accurately ascertain the time of onset? As noted, we saw a child in whom albuminuria was found during a routine examination. Edema was first noted six weeks later.

Before the introduction of sulfonamides and antibiotics, most children died early of acute infections. Those who survived the infection would often have diuresis

with disappearance of visible edema. The subsequent course of the illness of some of these children after such infection was (1) complete recovery, (2) recovery except for persistent albuminuria, (3) apparent recovery for many months, with a return of the nephrotic syndrome, and (4) no effect on the course of the disease.

Since the introduction of chemotherapy, recovery from intercurrent infection is more frequent and the children have a longer span of life. However, the chance of recovery, according to our experience, has not increased. Previously 80% of the deaths occurred during the first year of illness. In our recent group only about 30% died during the same period.

It has been our impression that, as a consequence of these abortive infections, diuresis now follows less frequently. Some patients who had been given chemotherapy repeatedly during infections have never experienced a true diuresis. They retained their edema until there was evidence of a chronic nephritis. Occasionally, when abdominal paracentesis was indicated there was subsequent loss of edema from other edematous sites. However, within a short time there was usually a return of the edema.

The reason for this failure of diuresis when chemotherapy interferes with the natural course of the infection is not clear. What occurred when the natural course of infection was not interrupted? What could be the consequences of this abortive infectious cycle? Jebens [16] has studied a group of scarlet fever patients in which penicillin was given early in the disease to some and later to others. When treatment was begun early in the disease, antibody formation was weak. Antibody formation was strong in those in whom treatment was begun later. The latter patients had more complications. Wannamaker, Rammelkamp, Denny, Brink, Houser, Hahn, and Dingle [17] have shown that if large doses of penicillin are given early during a Streptococcus infection the formation of antibody is inhibited. This is related in some degree to the inhibition of the Streptococcus (antigen). The antistreptolysin titer of the sera collected was lower in the treated patients than in the controls.

Are there any criteria during the course of lipid nephrosis that may aid in expressing an opinion as to outcome? We had the impression that if nephrotic symptoms persisted over years the prognosis was poor. This is true in the main, but, as shown in this series, there were children who showed improvement and even recovery after two years, and in one instance after eight years. We believed a rapidly recurrent anemia requiring frequent transfusions, even early in the disease, was of poor prognostic import.

A persistent azotemia early in the syndrome was also a bad omen. An occasional increased nonprotein nitrogen retention was not necessarily indicative of extensive renal damage. We feel that as long as there is no evidence of persistent azotemia the prognosis is not hopeless. It must be remembered that some children on a high protein diet and a low urinary output have an increased blood urea nitrogen. This

16. Jebens, H.: Gesichtspunkte zur Penicillinbehandlung des Scharlachs, unter besonderer Berücksichtigung der verbleibenden Ansteckungsfähigkeit und Immunität, Ztschr. Kinderh. **68**:303 (July 24) 1950.

17. Wannamaker, L. W.; Rammelkamp, C. H.; Denny, F. W.; Brink, W. R.; Houser, H. B.; Hahn, E. D., and Dingle, J. H.: Prophylaxis of Acute Rheumatic Fever by Treatment of the Preceding Streptococcal Infection with Various Amounts of Depot Penicillin, Am J. Med. **10**:673 (June) 1951.

increase can often be reduced if the protein in the diet is lowered. A rapid reaccumulation of edema fluid after abdominal paracentesis was not of prognostic import.

The significance of moderate hypertension was not clear. Persistent hypertension accompanied by azotemia had a poor prognostic import. However, if hypertension was present without azotemia, even for several years, the pressure often returned to normal.

Albuminuria persisting for years, when a child had clinically recovered and was leading a normal life, was not indicative of a short life span.

SUMMARY

A report on 21 patients with the nephrotic syndrome, followed from 4 to 26 years after onset, is presented.

The course of the illness before and after the introduction of the sulfonamides and antibiotics is noted.

The recovery rate, complete or partial, was about the same in the two groups. However, because of the effect of chemotherapy on infections, the later group had a longer span of life.

Death occurred in 36 cases, in 21 of which necropsies were obtained. The necropsy findings before and after the introduction of sulfonamides and antibiotics are discussed.

Possible etiological factors and rationale of treatment are presented.

STUDIES IN SICKLE CELL ANEMIA

Inheritance Factor, Including Effect of Interaction of Genes for Sicklemia and Thalassemia

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THE HEREDITARY nature of the sickling of erythrocytes of certain persons has been recognized and accepted for many years. The exact pathogenesis of the genetic pattern, however, has been the source of controversy. Earlier investigators [1] recognized no genetic difference between sickle cell disease and the asymptomatic trait (sicklemia). They regarded both conditions as being due to a single dominant gene which in some persons produced active disease and in others only an asymptomatic trait.

More recently, Neel [2] and Beet [3] have taken issue with the older hypothesis and have presented an alternative concept. According to these workers, the asymptomatic sickle cell trait is due to a gene which is represented but once in the patient's genetic system (heterozygous state), whereas active sickle cell disease appears when the gene occurs twice (homozygous state).

Moreover, the earlier investigators often found the sickling phenomenon lacking in the blood of one parent of children with the disease. On the other hand, Neel [2] finds that the blood of both biological parents of persons with the disease will consistently show the sickling trait when properly examined.

Because of these conflicting opinions expressed in the literature, we wish to report our results obtained by the examination of blood of parents of children who were known to have sickle cell anemia. These findings have a bearing upon the validity of the hypothesis of the homozygous-heterozygous genetic system of Neel [2] and Beet.[3]

From the Department of Pediatrics, Howard University College of Medicine, and the Pediatric Service of Freedman's Hospital.

1. Taliaferro, W. H., and Huck, J. G.: The Inheritance of Sickle Cell Anemia in Man, Genetics **8**:594, 1923.

2. (*a*) Neel, J. V.: Inheritance of Sickle Cell Anemia, Science **110**:64 (July 15) 1949; (*b*) The Inheritance of the Sickling Phenomenon, with Particular Reference to Sickle Cell Disease, Blood **6**:389 (May) 1951.

3. Beet, E. A.: Genetics of Sickle Cell Trait in Bantu Tribe, Ann. Eugenics **14**:279 (June) 1949.

METHOD

Five milliliters of blood was drawn by venipuncture and put immediately into a bottle which contained 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate. Six slides for examination for sickling were made on each subject tested. Two specimens were prepared by placing a drop of blood on a slide and sealing the moist preparation with petrolatum beneath a coverslip. These slides were examined for sickling at intervals of 24, 48, and 72 hours. This technique is referred to hereafter as the simple method. On two additional slides a drop of blood and a drop of broth culture of Bacillus subtilis [4] were mixed and sealed with petrolatum beneath a coverglass. A third specimen of two slides was similarly prepared by mixing a drop of fresh 2% sodium bisulfite solution and a drop of blood.[5] The slides of the last two methods

TABLE 1.—*Results of Testing for Sickling in Other Members of the Families*

Relative	No.	No. Tested	Sickling Trait Present	Sickling Trait Absent	Sickle Cell Disease
Mothers	16	14	13	1	0
Fathers	16	11	11	0	0
Siblings of 14 patients	41	35	15	18	2

TABLE 2.—*Hematologic Data on the Families of Sickle-Cell-Anemia Patients*

	Parents		Siblings	
	Mothers	Fathers	Sickling Trait	No Trait
Red blood cell count				
Highest	5.05	5.10	4.53	4.73
Lowest	3.78	3.89	3.45	3.12
Average	4.23	4.51	4.09	4.10
Hemoglobin, gm.				
Highest	14	16.2	13	14.5
Lowest	10	10.6	10.6	11
Average	13	13.6	12.1	12
Hematocrit reading				
Highest	53	49	46	45
Lowest	33	37	32	30
Average	39	44	39	40
White blood cell count				
Average	8,050	7,200	7,000	6,400

were observed for sickling after periods of 15 and 30 minutes. We considered the result for any subject as positive whose blood showed sickling on any of the six slides. A parent whose erythrocytes failed to exhibit sickling during the initial study by these methods was subsequently reexamined by the same procedures. The results of testing for sickling in other members of the families of patients known to have sickle cell anemia are recorded in Table 1.

The average number of siblings per family was 3.5. The patient with sickle cell anemia was the only child in two instances. Of the 16 families, there were 2 in which multiple cases of the disease occurred. There were two sets of twins in the series. The identical pair did not show sickling. Of the fraternal twins of another family, the girl had sickle cell anemia, while the boy showed only the trait. None of the parents of children with sickle cell anemia

4. Singer, K., and Robin, S.: Rapid Test for Demonstration of Sickle Cells and Its Clinical Significance, J. A. M. A. **136**:1021 (April 17) 1948.

5. Daland, G. A., and Castle, W. B.: Simple and Rapid Method of Demonstrating Sickling of Red Blood Cells: Use of Reducing Agents, J. Lab. & Clin. Med. **33**:1082 (Sept.) 1948.

had the disease. All the parents denied having had knowledge of the symptoms and signs of sickle cell anemia at any time in their lives. Data obtained from blood studies on parents and siblings of patients with sickle cell anemia are recorded in Table 2.

COMPARISON OF METHODS OF SICKLING

All the slides were made and observed by one of us (L. O. B.). The data obtained by the three methods previously described are listed in Table 3. The incidence of positive results was about equal with the B. subtilis and with the bisulfite method, both of which were more reliable than the simple technique for eliciting sickling.

It is to be noted from Table 3 that sickling was not demonstrated on the first attempt in five parents. Only after further attempts could sickling be elicited in four of them. Some of the earlier reports of the absence of sickling in parents of patients with sickle cell anemia may be attributed in part to failure of the authors to examine several specimens for sickling.

TABLE 3.—*Comparison of Three Methods Used for Detection of Sickling in the Blood of Parents*

	Bacillus Subtilis Culture	Sodium Bisulfite	Simple
No. on 1st test	25	25	25
Positive results	20	19	12
No. on 2d test	5	5	5
Positive results	4	4	3

COMMENT

There was one parent (mother of a child who clinically had sickle cell anemia) whose blood consistently did not sickle. Her blood was examined on eight different occasions by the following methods: simple moist preparation, B. subtilis method,[4] bisulfite method,[5] and the combined techniques of Scriver and Waugh[6] (venous stasis) and Hansen-Pruss[7] (vital dyes), as well as by exposures to carbon dioxide gas. A total of 60 slide specimens prepared by these various techniques failed to show any evidence of sickling.

The hemogram of this mother revealed an erythrocyte count of 4,590,000, a hemoglobin value of 10.6 gm., a hematocrit reading of 41, a white cell count of 7,250, and a reticulocyte count of 0.5%. The differential count revealed 59% neutrophiles, 37% lymphocytes, 2% monocytes, 1% eosinophiles, and 1% basophiles. The color index was 1.02; the volume index, 0.98; the mean corpuscular hemoglobin, 23 γ; the mean corpuscular volume, 89 cu.μ, and the mean corpuscular hemoglobin concentration, 25%. Peripheral smears of the blood revealed poikilocytosis, anisocytosis, numerous target cells, and hypochromia (Fig. 1). Fragility studies showed that hemolysis began at 0.50% hypotonic saline and ended at 0.14%. It was our opinion that this mother possessed the thalassemia trait.

The alkaline denaturation value as determined by Singer[8] was 1.7%, which is at the upper limit of normal. Carbon monoxide hemoglobin prepared from the mother's erythrocytes

6. Scriver, J. B., and Waugh, T. R.: Studies on Case of Sickle Cell Anemia, Canad. M. A. J. **23**:375 (Sept.) 1930.

7. Hansen-Pruss, O. C.: Experimental Studies of Sickling of Red Blood Cells, J. Lab. & Clin. Med. **22**:311 (Dec.) 1936.

8. Singer, K.: Personal communication to the authors.

was analyzed electrophoretically in cacodylate-sodium chloride buffer of pH 6.5 and ionic strength 0.1. Under these conditions, it is not possible to distinguish normal and thalassemia-trait hemoglobins.[9]

The normal electrophoretic pattern is further proof that this parent lacked the sickle cell trait. According to Wells and Itano,[9b] sickle-cell-trait hemoglobin contains 24 to 45% sickle-cell hemoglobin component. Electrophoretically, the hemoglobin of persons with the sickle cell trait is demonstrated as having two peaks.

The father is dead, but since the child exhibits sickling one can assume that the father must have possessed the sickling trait.

The patient, a 15-year-old boy, has been admitted to the hospital on numerous occasions over a six-year period for typical crises of sickle cell anemia. The crises have been characterized

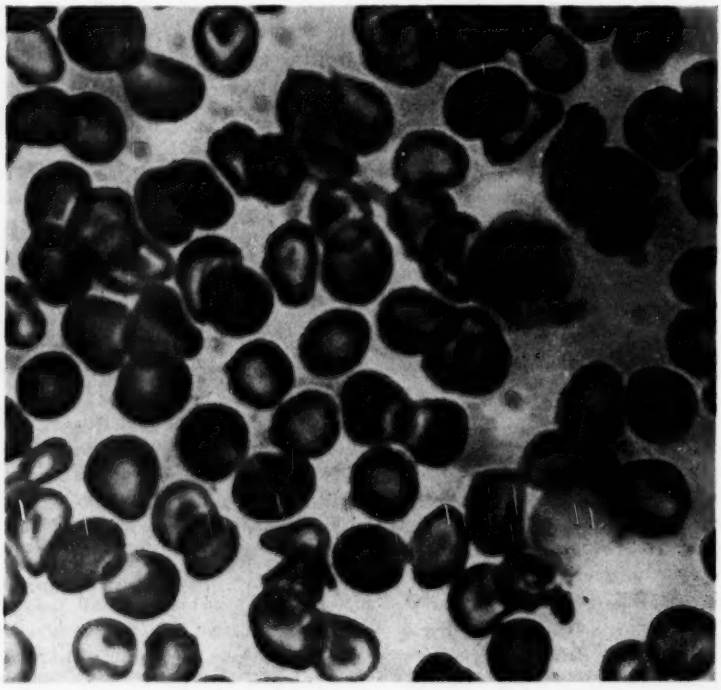

Fig. 1.—Blood smear of nonsickling mother of patient with sickle cell anemia. The specimen shows poikilocytosis, anisocytosis, target cells, and hypochromia. Hematological, chemical, and electrophoretic studies excluded sickle cell disease. She exhibits thalassemia minor (trait).

by joint, abdominal, and low-back pains and by jaundice, pallor, and weakness. The sickling phenomenon was readily demonstrated on each of these admissions (Fig. 2). The anemia has been rather severe, the red cell count being as low as 1,900,000 and the hemoglobin value 5.2 gm. per 100 cc. on one occasion. On 10 admissions the average red blood cell count was 2,600,000 and the hemoglobin 6.4 gm. per 100 cc. Electrophoretic analysis by Itano revealed that the patient's hemoglobin contained about 83% sickle-cell hemoglobin and about 17% hemoglobin having the same mobility as normal hemoglobin. The electrophoretic picture of

9. (*a*) Itano, H.: Personal communications to the authors. (*b*) Wells, I. C., and Itano, H. A.: Ratio of Sickle Cell Anemia Hemoglobin to Normal Hemoglobin in Sicklemias, J. Biol. Chem. **188**:65 (Jan.) 1951. (*c*) Itano, H. A., and Neel, J. V.: A New Inherited Abnormality of Human Hemoglobin, Proc. Nat. Acad. Sc. **36**:613 (Nov.) 1950.

persons of thalassemia-trait hemoglobin and that of normal hemoglobins are very similar and are difficult, if not impossible, to distinguish from each other. The pattern of the patient's hemoglobin is similar to that of one of the patients reported by Itano and Wells[9b] and to that of another patient who is heterozygous for the thalassemia and sickle cell traits.[10]

A younger female sibling has a normal hematological picture, and examination of her blood does not show the sickling phenomenon, target cells, or abnormal fragility.

In regard to the apparent exception to the hypothesis of homozygous-heterozygous inheritance, namely, that both parents of a child with sickle cell disease or one parent of a child with the sickle cell trait must exhibit sickling, Neel[11] offers the following explanations after excluding technical errors: (1) that in certain

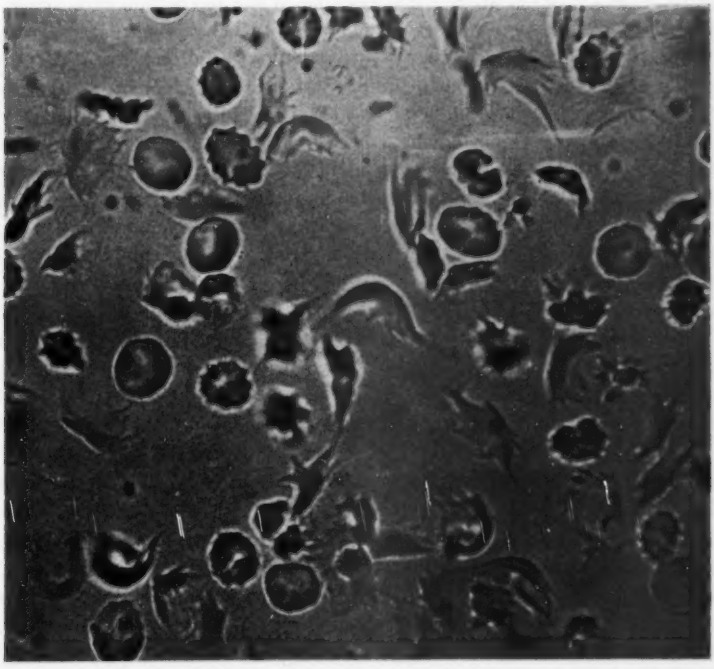

Fig. 2.—Photomicrograph of moist preparation of blood of boy whose mother has thalassemia minor. The specimen shows erythrocytes in various stages of sickling. All clinical and laboratory findings were compatible with the diagnosis of sickle cell anemia.

persons who are heterozygous for the sickling gene, that gene fails to find any expression; (2) that the legal parent is not the biological parent; (3) that that which appears to be sickle cell disease is actually due to the interaction of a single gene for the sickling phenomenon with as yet unknown environmental or genetic factors, or (4) that the apparently normal parent(s) has (have) actually contributed a sickle-cell gene to one or more of his (their) offspring in consequence of a mutation occurring at some stage in the formation of the gametes. The

10. Sturgeon, P.; Itano, H. A., and Valentine, W. N.: Chronic Hemolytic Anemia Associated with Thalassemia and Sickling Traits, Blood, to be published.

11. Neel.[2b] Neel, J. V.: Personal communication to the authors.

acceptance of these conditions would seem to render the apparent exceptions compatible with the hypothesis of homozygous-heterozygous inheritance. However, these exceptional cases warrant exhaustive study, because universal acceptance of Neel's hypothesis regarding the inheritance of sickling is contingent upon their complete elucidation.

Clinically, our exceptional case is indistinguishable from typical cases of sickle cell anemia. However, on a genetic basis, if we accept Neel's hypothesis that both parents of a patient with sickle cell anemia must exhibit sickling, this case cannot be accepted as an authentic example of this blood dyscrasia. This case appears to lie in Group 3 in Neel's explanation for exceptions to the rule, i. e., that that which appears to be sickle cell disease is actually due to the interaction of a single gene for the sickling phenomenon with as yet unknown environmental or genetic factors. It would now appear that the mating of one parent with the sickle cell trait and the other with the thalassemia trait can produce offspring which have a disease indistinguishable from sickle cell anemia. Powell, Rodarte, and Neel [12] reported the case of a Sicilian man with chronic hemolytic anemia associated with sickling which was indistinguishable from sickle cell anemia. The patient's father possessed the sickling trait and the mother the thalassemia trait. The two offspring of the patient and his normal wife possessed the thalassemia trait. The patient's brother's mating with a normal woman produced three children, two of whom exhibited the sickling phenomenon.

The paper of Powell and associates [12] is the first report of the segregation of sickle-cell-trait and thalassemia-trait genes in this country. The second case in the United States was that of an 8-year-old white girl of Sicilian descent reported by Wasserman, Phelps, and Hertzog.[13] Silvestroni and Bianco [14] reported eight similar cases in Italy. Our case is the first to be reported, to our knowledge, of the segregation of these genes in Negroes. Physicians are alerted to the possibility that thalassemia minor (trait) and thalassemia major (Cooley's anemia) can occur in Negroes.[15]

Another explanation for the exception to the theory of homozygous-heterozygous inheritance has appeared in the literature. Itano and Neel [9c] have reported a new inherited hemoglobin abnormality in nonsickling parents of patients with sickle cell disease. The component as demonstrated electrophoretically was different from that of the sickle cell trait. The interaction of the genes for the abnormal hemoglobin

12. Powell, W. N.; Rodarte, J. G., and Neel, J. V.: Occurrence in Family of Sicilian Ancestry of Traits for Both Sickling and Thalassemia, Blood **5**:887 (Oct.) 1950.

13. Wasserman, C. F.; Phelps, V. R., and Hertzog, A. J.: Chronic Hemolytic Anemia in White Child Due to Thalassemia and Sicklemia, with a Genealogic Survey, Pediatrics **9**:286 (March) 1952.

14. Silvestroni, E., and Bianco, I.: Una nuova entità nosologica: "la malattia microdrepanocitica," Haematologica **29**:455, 1946; Singolare associazione di "anemia microcitica costituzionale" con "drepanocito-anemia" in sogetto di razza bianca, Policlinico (sez. prat.) **53**:265 (April 28) 1946; Un nuovo caso di malattia microdrepanocitica, ibid. **55**:1207 (Oct. 4) 1948.

15. Dameshek, W.: Familial Mediterranean Target-Oval Cell Syndromes, Am. J. M. Sc. **205**:643 (May) 1943. Schwartz, S. O., and Mason, J.: Mediterranean Anemia in Negro: A Report of 4 Cases and Their Families, Blood **4**:706 (June) 1949. Stiles, M. H.; Manlove, C. H., and Dangerfield, C. D.: Mediterranean Anemia: Report of Case in Negro, Northwest Med. **45**:23 (Jan.) 1946.

pattern and the sickle cell trait can produce children with a hematological picture which resembles sickle cell anemia but is of less severity. Kaplan, Zuelzer, and Neel [16] state that this form of sickle cell disease is characterized by a mild hemolytic anemia with slowly progressive splenomegaly in the absence of cardiac or musculoskeletal manifestations. Reticulocytosis is slight, and icterus is not observed. On the other hand, the interaction of the sickle-cell-trait gene with that of the thalassemia-trait gene, as occurred in our case, seems to produce children with a clinical and hematological picture indistinguishable from that of sickle cell anemia.

It has been shown that the sickling trait is commoner in Africans (six investigators report an average of 12.6% or higher,[17] as opposed to the 7% reported for the American Negro). Contrariwise, sickle cell anemia is rarer in Africa, in contrast to the reported 0.14% found in the American-Negro population.[17b] These findings would seem to be in disagreement with the present concepts of the inheritance of sickle cell anemia, but might be explained by the observations that sickling occurs more frequently in light-skinned Negroes than in the dark types.[18] Raper [17b] suggests that the appearance of sickle cell anemia may depend on some factor imported by marriage with persons other than Africans. Hodges [17a] found that the incidence of sickling increased with the dilution of the Negro blood by small amounts of white and American-Indian blood. Further, he observed that the increased incidence is limited to those mixtures which contain approximately five-eighths or six-eighths Negro blood. None of the persons with sickle cell anemia in his study were less than five-eighths Negro. The rarity of this blood dyscrasia in Africans and the common occurrence in the American Negro whose blood is mixed would seem to suggest that dilution potentiates the sickling gene and contributes to the production of the clinical state of sickle cell anemia.

Our results from sickling studies of the parents of patients with sickle cell anemia are in general compatible with the hypothesis of homozygous-heterozygous inheritance and tend to substantiate the findings of Neel. From the mating of 32 parents there were 57 offspring, of whom 18 had sickle cell anemia, 15 the sickle cell trait, and 18 were normal. Since six siblings were not tested, and since those who were available were tested only once, perhaps the incidence of familial sickling is higher than represented.

As was anticipated, no evidence of sickle cell disease was found in any of the parents tested. Although the fertility of persons with sickle cell anemia is apparently low,[19] the advent of antibiotics has improved the general prognosis in the disease, and it is likely that more children will attain adulthood and potential parenthood.

16. Kaplan, E.; Zuelzer, W. W., and Neel, J. V.: Studies Concerning a New Inherited Abnormality of Hemoglobin, Abstracts of Society for Pediatric Research, Atlantic City, May 2, 3, 1951, p. 10.

17. (*a*) Hodges, J. H.: Effect of Racial Mixtures upon Erythrocytic Sickling, Blood **5**:804 (Sept.) 1950. (*b*) Raper, A. B.: Sickle Cell Disease in Africa and America: Comparison, J. Trop. Med. **53**:49 (March) 1950.

18. Diggs, L. W.; Ahmann, C. F., and Bibb, J.: Incidence and Significance of Sickle Cell Trait, Ann. Int. Med. **7**:769 (Dec.) 1933.

19. Turner, C. M.: Sickle Cell Anemia in Pregnancy: Resumé of Literature, with a Case Report, J. Nat. M. A. **43**:165 (May) 1951.

In testing for the sickling phenomenon in the parents of children with sickle cell anemia, it is important to repeat the tests if they are negative. The blood of 20% of the parents tested in our series did not show sickling on the first attempt, whereas 4% only failed to show the trait on the second attempt.

SUMMARY

The families of 16 patients with sickle cell anemia have been investigated for sickling.

1. Of the 25 parents tested, 24 showed the sickling trait. None had sickle cell anemia.

2. Of the 57 offspring in the study, 18 had the disease, 15 had the trait, 18 were normal, and 6 were not tested.

Our findings with one exception are compatible with the genetic hypothesis advanced by Neel for the inheritance of sickling.

The blood of the mother of one patient failed to sickle on repeated testing with various methods. This parent's blood on electrophoretic analysis failed to exhibit the pattern characteristic of sickle-cell-trait hemoglobin. The hematological findings in this mother were consistent with those commonly seen in persons with thalassemia minor. Our observation in this case, as well as the reports of other workers, indicates that the mating of a person carrying the sickling trait with another person bearing the thalassemia trait can result in a disease in the offspring indistinguishable from sickle cell anemia.

Dr. Harvey A. Itano, of the California Institute of Technology, Pasadena, Calif., performed the electrophoretic analyses reported in this article.

Dr. Karl Singer, of the Michael Reese Hospital, Chicago, performed the alkaline denaturation studies.

PHYSIOLOGICAL AVAILABILITY OF VITAMIN A FROM CAPSULES

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AND
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BROOKLYN

CONTROL procedures for vitamin-containing pharmaceutical products are based on conformance of analytical values with the labeled statement. The physician and nutritionist are interested in the physiological availability in addition to labeled contents. In recent years, the importance of physiological availability, rather than analytical content, has been repeatedly emphasized.[1] Oser and associates [2] have indicated that "the nature of precautions taken to insure stability of vitamins in pharmaceutical capsules or tablets which are usually swallowed whole raises the question of physiological availability of the vitamins." They have shown that a given amount of thiamine in one capsule is four times as available in another capsule. Some pharmaceutical preparations contained riboflavin rendered so insoluble as to be physiologically unavailable.[3] Thiamine was found to be relatively unavailable from live yeast.[4]

The availability of the fat-soluble vitamins, particularly vitamin A, in liquid media has been the subject of intensive study since it was shown that acute deficiency of vitamin A may exist, as a result of impaired absorption in a number of diseases, when the vitamin is given orally in oil.[5] Such defects may be overcome when the vitamin is given in aqueous dispersions.[6] However, while the availability of vitamin

From the Department of Biochemistry, Jewish Hospital.

1. Melnick, D., and Oser, B. L.: Physiological Availability of the Vitamins, Vitamins & Hormones **5**:39, 1947. Kline, O. L.: Estimation of Vitamins: A Human Assay for Physiological Availability, Biol. Symposia **12**:524, 1947.

2. Oser, B. L.; Melnick, D., and Hochberg, M.: Physiological Availability of the Vitamins: Study of Methods for Determining Availability of Vitamins in Pharmaceutical Products, J. Indust. & Engin. Chem., Anal. Ed. **17**:405, 1945.

3. Oser, B. L.; Melnick, D., and Rader, M.: Estimation of Vitamin A in Food Products, J. Indust. & Engin. Chem., Anal. Ed. **15**:724, 1943.

4. Hochberg, M.; Melnick, D., and Oser, B. L.: Physiological Availability of the Vitamins: Inefficiency of Live Yeast as Source of Thiamine, J. Nutrition **30**:201, 1945.

5. Sobel, A. E.: The Problem of Absorption and Transportation of the Fat-Soluble Vitamins, Vitamins & Hormones, to be published.

6. (*a*) Sobel.[5] (*b*) Kramer, B.; Sobel, A. E., and Gottfried, S. P.: Serum Levels of Vitamin A in Children: Comparison Following the Oral and Intramuscular Administration of Vitamin A in Oily and Aqueous Mediums, Am. J. Dis. Child. **73**:543, 1947. (*c*) Lewis, J. M.; Bodansky, O.; Birmingham, J., and Cohlan, S. Q.: Comparative Absorption, Excretion, and Storage of Oily and Aqueous Preparations of Vitamin A, J. Pediat. **31**:496, 1947. (*d*) Lewis, J. M.; Cohlan, S. Q., and Messina, A.: Further Observations on the Absorption of Vitamin A: Influence of the Particle Size of the Vehicle on the Absorption of Vitamin A, Pediatrics **5**:425, 1950. (*e*) Popper, H., and Volk, B. W.: Intestinal Absorption of Vitamin A

(Footnote continued on next page)

A from a liquid menstruum has been studied, the physiological availability of fat-soluble vitamins from pharmaceutical capsules has received no attention. Many older children and adults find the flavor of aqueous dispersions objectionable. Thus, the physician is faced with the problem when vitamin supplementation is indicated, particularly in cases of impaired absorption, of prescribing a capsule which is most likely to assure physiological availability. This investigation was undertaken to provide some facts in answer to the many questions raised by physicians in this hospital and elsewhere.

Since it was beyond the scope of this study to examine all available preparations, we selected three multivitamin capsules, made by different manufacturers, which are in wide use in our community. As will be seen from the results of this study, the desirability of determining physiological availability of the fat-soluble vitamins is indicated.

The method of testing physiological availability was the vitamin-A tolerance test, which consists of measuring the changes in blood vitamin A following administration

TABLE 1.—*Composition of Three Multivitamin Capsules and Reference Oil*

Component	Capsule *			Reference Oil Units/ Gm.
	A	B	C	
Vitamin A, U. S. P. units	5,000	5,000	5,000	60,000
Vitamin D, U. S. P. units	500	500	500	8,500
Ascorbic acid, mg.	60	37.5	50	.....
Thiamine mononitrate, mg.	3	.....	5	.....
Thiamine hydrochloride, mg.	.....	2.5	.....	.....
Riboflavin, mg.	2 †	2.5	5	.....
Nicotinamide, mg.	20	20	20	.....
Pantothenyl alcohol (panthenol®), mg.	5	.....	.....	.....
Calcium pantothenate, mg.	.....	5	5	.....
Pyridoxine hydrochloride, mg.	0.3	0.5	0.5	.....
Tocopherol, mg.	2	.....	.....	.....
dl, α-tocopheryl acetate, mg.	.....	.....	1	.....
Vitamin B_{12}, μg.	.....	.....	1	.....

* Capsule A was vifort®; capsule B, unicaps®; capsule C, "vi-aqua." Reference oil was percomorph liver oil (oleum percomorphum).

† Schoen, K., and Gordon, S. M.: Water-Soluble Methylol Derivatives of Riboflavin, Arch. Biochem. **22**:149, 1949.

of a standard dose. That this is a valid test of availability was shown in studies comparing the absorption of aqueous vitamin A with that of oily vitamin A in which higher blood levels were obtained with corresponding amounts of aqueous vitamin A. Objective evidence in human subjects and in animals indicated that increased blood levels represent increased total absorption. This was shown in balance studies,[6c,d] increased liver storage[7] in rats, and higher transfer of vitamin A to milk.[8] Final

from Aqueous and Oily Menstruum, Proc. Soc. Exper. Biol. & Med. **68**:562, 1948. (*f*) Sobel, A. E.; Besman, L., and Kramer, B.: Vitamin A Absorption in Newborns, Older Children, Adults, and Storage in Rats, abstracted, Federation Proc. **7**:189, 1948. (*g*) Sobel, A. E., and Rosenberg, A. A.: Vitamin A Storage of Sucklings Following Administration to the Dams of Vitamin A in Oily and Aqueous Media, J. Nutrition **42**:557, 1950.

7. (*a*) Lewis, Bodansky, and others.[6e] (*b*) Sobel, A. E.; Sherman, M.; Lichtblau, J.; Snow, S., and Kramer, B.: Comparison of Vitamin A Liver Storage Following Administration of Vitamin A in Oily and Aqueous Media, J. Nutrition **35**:225, 1948.

8. Sobel, A. E.; Rosenberg, A. A., and Kramer, B.: Enrichment of Milk Vitamin A in Normal Lactating Women: Comparison Following Administration of Vitamin A in Aqueous and Oily Mediums, Am. J. Dis. Child. **80**:932, 1950.

TABLE 2.—*Comparison of Serum Vitamin A Levels in Normal Adults Using Capsules A, B, and C, and Reference Oil.*

		Vitamin A, Expressed in γ per 100 Ml. of Serum					
Case No.	Preparation	Fasting	3 *	6 *	9 *	24 *	Maximum Rise
1	Capsule A	48	302	96	86	62	254
	Capsule B	42	80	105	80	42	63
	Capsule C	40	77	87	65	64	47
	Reference oil	59	178	135	79	63	119
2	Capsule A	48	112	271	119	55	223
	Capsule B	54	214	140	74	64	160
	Capsule C	63	146	98	78	64	83
	Reference oil	35	175	145	71	39	140
3	Capsule A	45	389	477	..	68	432
	Capsule B	42	231	213	..	..	189
	Capsule C	53	67	181	67	55	128
	Reference oil	63	82	278	..	..	215
4	Capsule A	38	210	115	23	..	172
	Capsule B	40	123	83	..	..	83
	Capsule C	49	75	63	54	50	26
	Reference oil	17	21	90	..	..	73
5	Capsule A	82	295	168	..	..	213
	Capsule B	63	215	111	83	..	152
	Capsule C	44	154	56	49	45	110
	Reference oil	51	56	56	56	..	5
6	Capsule A	38	165	56	56	60	127
	Capsule B	37	97	110	108	87	73
	Capsule C	37	74	65	58	60	37
	Reference oil	27	55	69	44	37	42
7	Capsule A	72	83	163	74	39	91
	Capsule B	39	152	78	83	78	113
	Capsule C	78	164	25	25	26	86
	Reference oil	48	48	52	140	72	92
8 †	Capsule A	53	333	373	..	63	320
	Capsule B	41	395	296	..	63	354
	Capsule C	56	184	150	107	56	128
	Reference oil	38	48	283	..	..	245
Mean	Capsule A	53	226	215	71	58	230
	Capsule B	45	188	142	86	66	148
	Capsule C	53	118	91	63	53	81
	Reference oil	42	83	139	78	53	116
9 †	Capsule A	44	343	65	48	48	190
	Capsule B	23	85	89	79	37	62
	Reference oil	44	110	232	49	45	188
10 †	Capsule A	30	158	93	..	52	128
	Capsule B	15	100	40	..	43	85
	Reference oil	38	60	48	48	47	22
11 †	Capsule A	46	..	123	..	60	77
	Capsule B	44	78	100	..	46	56
	Reference oil	40	120	373	..	63	333
12 †	Capsule A	65	575	195	..	70	510
	Capsule B	56	367	220	..	76	311
Over-all	Capsule A	51	270	183	68	58	229
Mean	Capsule B	41	178	132	85	59	142

* Number of hours after administration of test dose.
† These subjects received 1,000 units per pound of body weight. All other subjects received 500 units per pound of body weight.

proof that the increase of blood and milk vitamin A represent increased absorption was shown by liver-storage studies on sucklings, who had four times as much vitamin A when the mother received vitamin A in aqueous dispersions as when the dose was given in oil.[6g]

EXPERIMENTAL PROCEDURE

The subjects of these tests were normal adults. Vitamin-A tolerance tests were performed by administering either 500 or 1,000 U. S. P. units of vitamin A per pound (1,000 or 2,000 U. S. P. units per kilogram) of body weight in the postabsorptive state. After this, the subjects consumed a normal diet except that vitamin-A- or carotene-containing foods were restricted. Blood specimens were taken prior to the test and 3, 6, 9, and 24 hours thereafter. The serum was saponified and analyzed for vitamin A by the method of Sobel and Snow.[9] The capsules were swallowed without chewing. Three multivitamin capsules of approximately the same composition were tested, Capsule A (vifort®), Capsule B (unicaps®), Capsule C ("vi-aqua"); and, as a reference of absorption, percomorph liver oil (oleum percomorphum) was employed (Table 1). Each of the three capsules was analyzed and found to agree within 3% of the stated values.

Eight adults were tested with all four of the above preparations at intervals of two days to a week. An additional three subjects were tested with three of the preparations, and one subject was tested with two of the preparations. The results are shown in Table 2, and the mean values for the eight patients who were tested with all four preparations are plotted in Chart 1, while the mean maximum rise for these eight subjects is shown in Chart 2.

The results indicate a far greater absorption with Capsule A than with Capsules B or C or with the reference oil. The maximum rise for Capsule A is 198% of that for the reference oil, while that for Capsule B is 128% of that for the reference oil, and the maximum rise for Capsule C is only 70%. The maximum rise for Capsule A is 284% of that for Capsule C.

COMMENT

The results obtained, although for only three of the innumerable varieties of capsules on the market, clearly indicate that great differences exist in the physiological availability of vitamin A from even widely used preparations. The maximum rise (Chart 2) for Capsule A was 198%, that for Capsule B was 128%, and that for Capsule C was only 70% of that for the reference oil. The maximum rise with Capsule A was 284% of that with Capsule C. These differences are of such magnitude that the desirability of testing the physiological availability in humans of capsules containing the fat-soluble vitamins, especially vitamin A, is clearly indicated. The method employed in this study is relatively simple, whereas balance studies are not only difficult but open to the objection that vitamin A may be readily destroyed in the gastrointestinal tract. The lack of fecal vitamin A by no means proves absorption.

In conditions such as the celiac syndrome, sprue, biliary deficiency, gastrectomy, liver disease, diarrhea, cretinism, chylous ascites, and some dermatological disorders,[5] in which vitamin supplementation is critical, percomorph liver oil is considered a poor source of vitamin A. A vitamin capsule that is actually below this oil in absorbability would be regarded as a very poor source of vitamin A. Since the subjects tested in the present study had normal absorption, these differences might be even greater in subjects whose absorption is impaired.

9. Sobel, A. E., and Snow, S. D.: The Estimation of Serum Vitamin A with Activated Glycerol Dichlorohydrin, J. Biol. Chem. **171**:617, 1947.

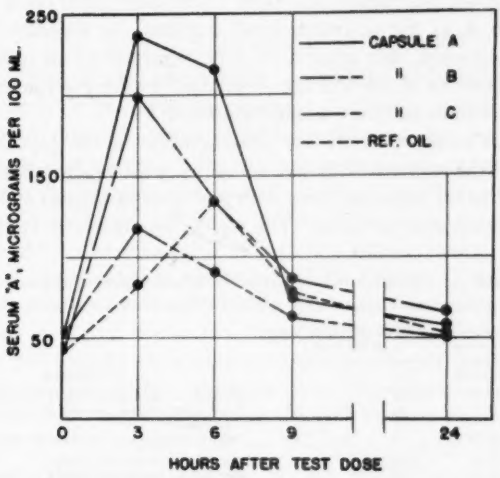

Chart 1.—Mean changes in serum vitamin A following the administration of capsules A, B, C, and the reference oil.

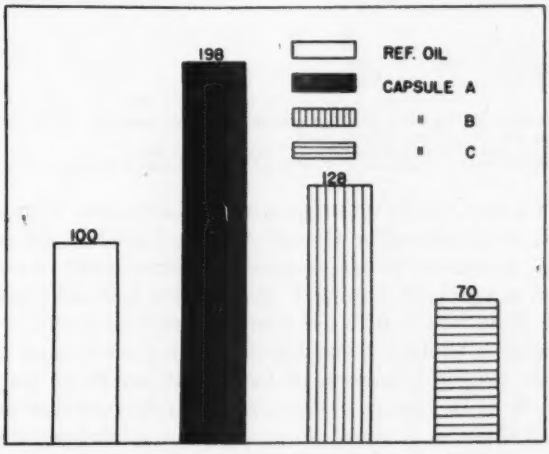

Chart 2.—Comparative mean maximum rise in serum vitamin A following the administration of capsules A, B, C, and the reference oil.

While many factors enter into the physiological availability of fat-soluble vitamins, three may be mentioned with a fair degree of certainty that they play a part. 1. The site at which the capsule releases its contents. Disintegration of the capsule should take place in the jejunum or above so that the contents may come in contact with that portion of the gastrointestinal tract where absorption takes place. 2. The stability of vitamin A in the gastrointestinal contents. In the case of vitamin A, which is readily destroyed, this must always be regarded as an important factor. 3. The state of dispersion of the vitamin A released to the gastrointestinal content. Finely dispersed particles are more readily absorbed.[10]

An attempt was made to study the disintegration of the capsules in aqueous media at the pH of the stomach with and without pepsin in physiological concentration, and at the pH of the intestinal tract with and without trypsin and chymotrypsin in normal physiological concentration. The results are shown in Table 3. Capsules

TABLE 3.—*Disintegration Studies of Multivitamin Capsules*

	Treatment		Disintegration Time in Seconds *			
Capsule	pH	Temperature	1	2	3	Comment
A	2.0	37 C.	>310	..	..	Swelled to approximately 3 × size; did not rupture †
B	2.0	37 C.	45	70	80	Gray precipitate; turbid red supernatant; oil on surface †
C	2.0	37 C.	2	15	30	Yellow precipitate; turbid red supernatant †
A	7.8	37 C.	>210	..	..	See data for pH 2 (above)
B	7.8	37 C.	8	..	..	Swelled to approximately 3 × size; did not rupture †
C	7.8	37 C.	3	..	..	Swelled to approximately 3 × size; did not rupture †
A	7.8	37 C.	2.5	30	40	Gray precipitate; clear brown supernatant
B	20 mg. per 100 cc. trypsin and 23 mg.		2.5	21	40	Surface oil phase; orange precipitate; turbid yellow supernatant
C	per 100 cc. chymotrypsin ‡		3.0	56	152	Yellow precipitate; clear red supernatant
A	2.4	.....	15	50	70	.....
B	20 mg./ml. of "1:		8	18	25	.....
C	10,000" pepsin (Parke, Davis & Co.)		8	>235	..	.....

* Column 1 indicates (1) beginning of disintegration of capsule covering; (2) spilling of contents into incubation medium, and (3) complete disintegration.
† Same treatment with mild agitation (Warburg) gave same results.
‡ Chymotrypsin and trypsin in physiological levels of duodenal juice according to Dr. H. Goldenberg.

A and B disintegrated rapidly with trypsin and chymotrypsin. With pepsin Capsule B disintegrated first, followed by Capsule A, while Capsule C did not disintegrate for four hours. In contrast to this, in aqueous medium devoid of enzymes, both at a pH of 2 and at a pH 7.8, Capsule C disintegrated first and Capsule A did not disintegrate at all in from four to five hours. From these results, it would appear that disintegration in solutions containing enzymes is a better index of physiological availability than solution in aqueous medium. It is remarkable that capsules may behave differently in an aqueous medium containing enzymes than in pure aqueous medium. Both Capsules A and C dispersed evenly on disintegration, to give an optically clear solution after centrifugation. Capsule B, however, showed a considerable oily layer. Whether the vitamin A was in the oily or the aqueous phase was not determined.

The above tests simply serve to emphasize the point made by Oser,[2] that disintegration studies, physical appearance, or analytical values are not reliable indices

10. Kramer, Sobel, and Gottfried.[6b] Lewis, Bodansky, Birmingham, and Cohlan.[6c] Sobel, Besman, and Kramer.[6f] Sobel, Sherman, Lichtblau, Snow, and Kramer.[7b]

of physiological availability. Until reliable test-tube indices of physiological availability are developed, one must recommend direct testing on human subjects when possible. It is hoped that this study will stimulate others to test the physiological availability of vitamin A from the numerous preparations on the market. Such studies will lead to the preparation of capsules of higher physiological availability.

SUMMARY

The need for studying the physiological availability of fat-soluble vitamins, more particularly vitamin A, from the pharmaceutical capsules is indicated. Vitamin A absorption tests in humans, under suitable conditions, can serve as an index of availability. Wide divergences in physiological availability can exist. Three typical multivitamin capsules of approximately the same composition were tested. When compared with the maximum rise for a reference test substance (percomorph liver oil), taken as 100%, the maximum rise in the blood vitamin A was 198% for Capsule A, 128% for Capsule B, and only 70% for Capsule C. When the maximum level for Capsule C was taken as 100%, the maximum rise for Capsule A was 284% and that for Capsule B was 183%. Disintegration studies and the state of dispersion of the contents provided no clear indication of physiological availability of vitamin A in the three capsules tested, although some correlation was found in media employing trypsin plus chymotrypsin, and pepsin. In pure aqueous media, both at pH 2 and at pH 7.8, the capsule with the lowest physiological availability disintegrated first, while the capsule with the highest physiological availability did not disintegrate for several hours.

APPARATUS FOR PROLONGED CONTINUOUS AEROSOL ADMINISTRATION

JOSEPH B. MILLER, M.D.
MOBILE, ALA.

ADMINISTRATION of a therapeutic agent by inhalation of its aerosol is an established procedure. Some medicinal aerosols, particularly wetting or humidifying agents, must be administered into a tent continuously for many hours or even several days for complete and effective therapy.

Many difficulties attend the use of ordinary methods of prolonged aerosol administration. The nebulizers in common use have a maximum capacity of only about 10 cc. of liquid; so an automatic and continuous source of additional liquid is required. This is achieved, basically, by inserting a needle through the side stopper of a nebulizer and dripping the therapeutic solution from a clysis bottle into the nebulizer through this needle.

This method is simple and would be ideal except that the fluid level is utterly impossible to control. No matter how carefully the rate of drip is measured, the nebulizer will either run dry or overflow ("rain") onto the patient in a short time. A study was attempted to determine the exact number of drops per minute necessary to maintain a constant fluid level at various rates of oxygen flow, but this balance was impossible to achieve. It is also the universal experience of nurses administering therapy by this method that, despite frequent and repeated readjustments of drip rate, the nebulizer is always alternating between a condition of "raining" on the patient or drying out completely.

I have tried a great many hook-ups and instruments and have devised an apparatus that overcomes these difficulties. It is based on the principle of constantly dripping an excess amount of solution into the nebulizer and constantly withdrawing all solution above a given optimum level.

The apparatus is built around an ordinary De Vilbiss #40 nebulizer.[1] The nebulizer is taped or clamped securely by its neck to the upright stem of a clysis standard (Fig. 1). From the horizontal limb of the standard is hung a 500 or 1,000 cc. clysis bottle (delivery bottle), containing the solution to be nebulized.

An empty quart or half-gallon can (such as is used for fruit juices or coffee) is then securely taped to the bottom of the upright stem of the standard. Into this can is placed an empty 500 or 1,000 cc. clysis bottle (collecting bottle), which is to collect the solution which overflows from the nebulizer. The full delivery bottle above and the empty collecting bottle below are then connected to the side opening (vent) of the nebulizer by means of a specially made 2-hole stopper.

Research Associate, Department of Biology, Spring Hill College.

1. The De Vilbiss #40 nebulizers employed in developing this instrument were supplied by Mr. Donald Fenstermaker and Mr. Phillip Bonesteel, The De Vilbiss Company, P. O. Box 552, Somerset, Pa.

The two-hole stopper is made from the rubber stopper which is provided by the manufacturer for the side vent of the nebulizer. The first step is to shorten the stopper by cutting ¼ in. (0.6 cm.) off the small end with scissors. A hypodermic needle, preferably size 19 or larger, is pushed through the stopper for its full length and then bent upward distally with pliers through an angle of 90 degrees. With an ordinary ampule file, a groove can be cut in the needle about ¼ in. from the bend, and the distal end of the needle can be snapped off with pliers. When this has been completed, a second needle is introduced and processed in the same manner, except that its opening points in the opposite direction (downward).

This two-hole stopper is then introduced into the side vent of the nebulizer. The spread of the needles makes it impossible to introduce the stopper directly, so one needle must be turned

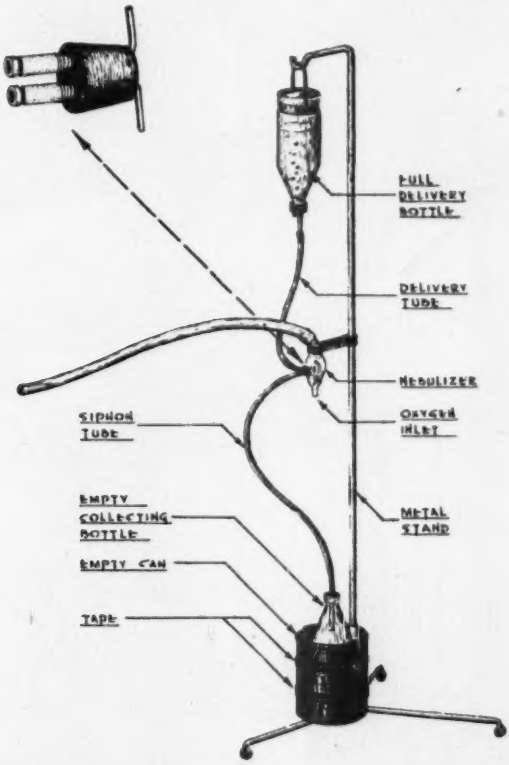

Fig. 1.—Diagram of apparatus employed for prolonged continuous aerosol administration. Insert shows details of two-needle stopper.

and held temporarily in the same direction as the other needle. After the stopper is thus introduced, the needles are again pointed in opposite directions, one upward, the other downward. The rubber stopper slides in more easily if it is moistened before introduction into the vent.

The plastic tubing (delivery tube) from the full bottle above is then connected to the uppermost needle of the stopper. A length of similar plastic tubing (siphon tube) is then run from the lower needle into the empty bottle below. The solution is allowed to drip from the upper bottle until it fills the nebulizer reservoir and is then regulated to at least 50 drops a minute.

The fluid will not overflow into the empty bottle spontaneously; it must be started manually (siphoned). This is accomplished by "stripping" the siphon tube downward. Two or three hand

squeezes in a progressively downward manner usually suffice; excessive stripping will empty the surplus solution from the nebulizer, draw air into the siphon tube, and cause a loss of the siphon effect.

Once the siphoning has been started, the weight of the continuously falling column of fluid in the siphon tube will keep the siphon going indefinitely. The only requirement is that the solution from the full bottle above be kept dripping continuously at a sufficiently rapid rate to

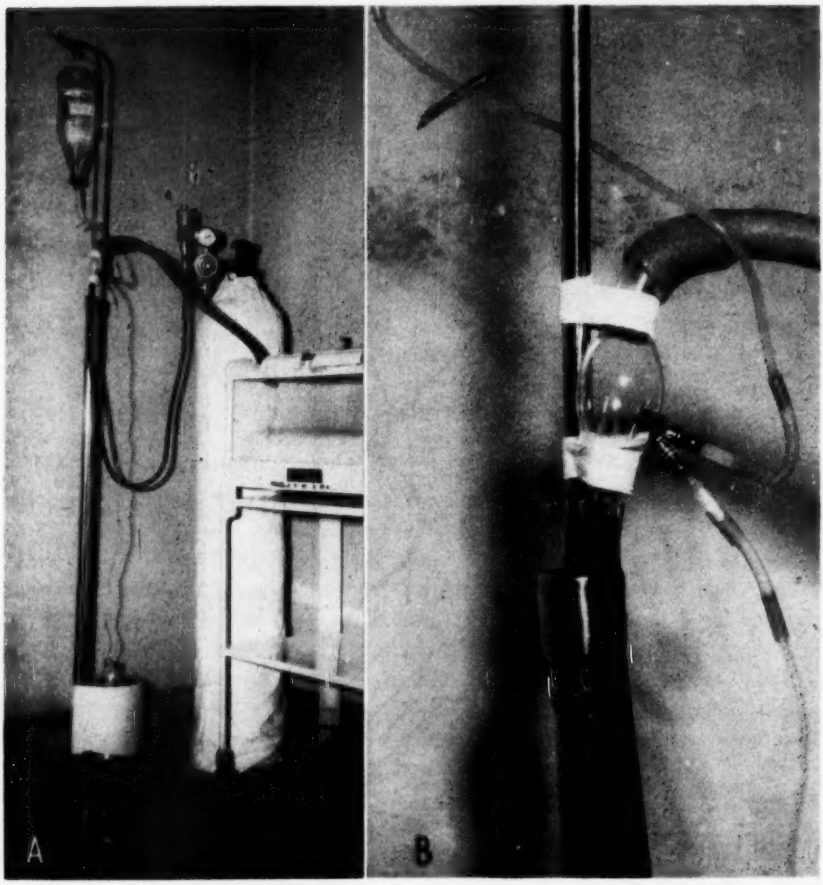

Fig. 2.—*A*, aerosol apparatus in use, showing method of supplying oxygen to incubator babies. *B*, close-up of nebulizer and its attachments.

keep refilling the nebulizer, so that the siphon tube will not "suck air." The level of solution in the nebulizer will always be constant; it can neither run dry nor overflow. When the top bottle becomes empty, it is refilled from the bottom bottle, and no wastage occurs. Refilling is required about every four to six hours when 500 cc. bottles are used, and every eight to twelve hours when 1,000 cc. bottles are used.

To prepare the apparatus for use, the oxygen tube is attached from the gauge to the oxygen inlet of the nebulizer, and the gauge is opened to permit a flow of 8 liters of oxygen a minute. Compressed air can be employed if the patient does not need oxygen.

The aerosol is then directed into the tent or incubator through a larger tube, ½ in. (1.3 cm.) in diameter and 3 ft. (92 cm.) in length, connected to the delivery end of the nebulizer. If two children are to be treated simultaneously, a large Y-tube is inserted in this line, so that two tubes can be run from one nebulizer. In this event, the oxygen (or air) flow must be doubled. Since the entire apparatus is attached to the standard, it can be brought into action by simply rolling the standard to the bedside (Figs. 2 and 3). In most cases no cleansing or sterilizing is required, since no part of the apparatus touches the patient.

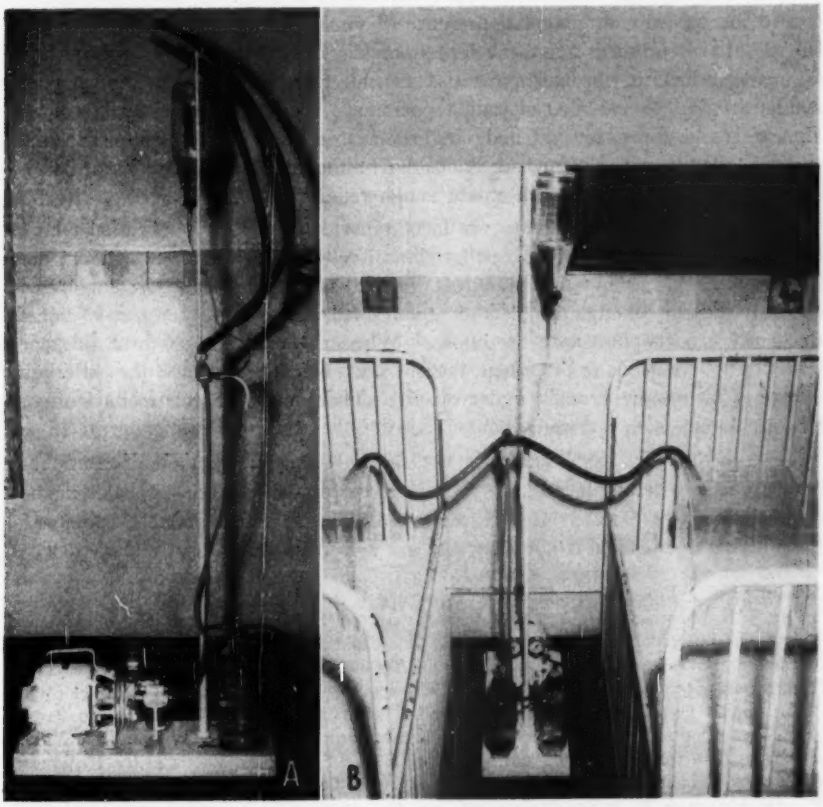

Fig. 3.—*A*, aerosol apparatus built onto platform with compressor-suction unit. This combination supplies the detergent aerosol without oxygen and provides an ever-present source of suction for secretions in nose, throat, or tracheotomy tube. Oxygen can be employed during an acute illness by attaching an oxygen line to the nebulizer; when oxygen is no longer needed, compressed air can be substituted. *B*, combined unit employed for treating two children simultaneously. High pressures obtainable with this unit allow for the production of a much denser and more copious aerosol mist than is ordinarily produced with oxygen.

COMMENT

The primary use of this apparatus is for the continuous nebulization of a detergent aerosol solution designed for dissolving viscid bronchopulmonary secretions.[2]

2. (*a*) Miller, J. B.: The Applicability of Surface-Active Agents in Aerosol Streptomycin Therapy of Pulmonary Tuberculosis, Quart. Bull. Sea View Hosp. **10**:155-160, 1948. (*b*) Hurwitz, C., and Miller, J. B.: Effect of Triton A-20 and pH Value on the Streptomycin

(Footnote continued on next page)

This detergent solution, "alevaire," [3] is unique in aerosol therapy in that it combines the desirable properties of total lack of toxicity with marked activity in lowering surface tension and viscosity. Out of a large group of detergents tested for aerosol therapy in laboratory, animal, and human studies, this was the only one which was completely inert, chemically stable, and free of any toxic side-effects whatsoever.[4]

This solution has been most employed for preventing respiratory obstruction due to the presence or potential presence of viscid bronchopulmonary secretions. Its uses have included treatment for spasmodic croup, laryngotracheobronchitis, asthmatic bronchitis, chronic bronchitis, bronchiectasis, bronchiolitis, bronchopneumonia, atypical pneumonia, aspiration pneumonia, neonatal atelectasis, fibrocystic disease, tracheotomy, foreign body in bronchi, pertussis, diphtheria, encephalitis and poliomyelitis with retained secretions due to intercostal or diaphragmatic paralysis, and comatose patients with absent cough reflex.

The details of clinical therapy are to be reported in another publication. However, it is necessary to state here that clinical response, while often striking, does not ordinarily occur in a few minutes. Several hours of therapy are required in order to deposit enough droplets of such small diameter to completely liquefy thickened bronchopulmonary secretions. When the tendency to form thickened secretions is recurrent or persistent, therapy must be continued until the underlying infectious factors are brought under control. Therefore, a reliable method of continuous nebulization is required.

The method described herein is not the only possible method of continuous aerosol therapy by any means, but it is the most versatile and most reliable method of all those tested to date. It is extremely inexpensive as compared to commercial humidifying devices and is not limited to use with plain water, as are many devices.

Sensitivity of a Resistant Strain of M. Tuberculosis, Am. Rev. Tuberc. **62**:91-98, 1950. (*c*) Miller, J. B.; Abramson, H. A., and Ratner, B.: Aerosol Streptomycin Treatment of Advanced Pulmonary Tuberculosis in Children, Am. J. Dis. Child. **80**:207-237, 1950. (*d*) Miller, J. B.; Abramson, H. A., and Ratner, B.: Cases of Advanced Childhood Pulmonary Tuberculosis Treated with Streptomycin Aerosol, Quart. Bull. Sea View Hosp. **11**:102-115, 1950. (*e*) Miller, J. B.: Special Techniques of Aerosol Therapy for Infants and Children, in Somatic and Psychiatric Treatment of Asthma, edited by H. A. Abramson, New York, Williams & Wilkins Company, 1951. (*f*) Miller, J. B., and Abramson, H. A.: Surface Anesthesia of the Respiratory Mucosa by Nebulization, Quart. Bull. Sea View Hosp. **11**:1-6, 1949. (*g*) Miller, J. B.; Mann, F., and Abramson, H. A.: A Method for Topical Anesthesia by Nebulization of Local Anesthetics, Dis. Chest **16**:408-419, 1949. (*h*) Miller, J. B.; Conyers, W. H., and Dinhoffer, N.: A Simple, Safe Bronchographic Technique for Children, J. Pediat. **36**:721-727, 1950. (*i*) Miller, J. B.; Dinhoffer, N., and Conyers, W. H.: A New Bronchographic Technique Employing Aerosol Anesthesia: Further Experiences in Children and Adults, Am. J. Roentgenol., to be published. (*j*) Miller, J. B.; Boyer, E. H.; Hamel, E. G.; Swan, J. L., and Kilgore, S. S.: A Low-Toxicity Detergent for Aerosol Use in Respiratory Diseases: Preliminary Report, Mendelian, pp. 69-70, June, 1951. (*k*) Miller, J. B., and Boyer, E. H.: A Nontoxic Detergent for Aerosol Use in Dissolving Viscid Bronchopulmonary Secretions, J. Pediat., to be published. (*l*) Miller, J. B.: New Uses of Aerosols in Children, Mendelian **21**:45-47, 1951.

3. "Alevaire" formerly known as aerosol solution No. 3 (an alkylaryl polyether alcohol) is available from Dr. J. B. Rice, Director of Research, Winthrop-Stearns, Inc., 1450 Broadway, New York.

4. (*a*) Miller and others.[2j] (*b*) Miller and Boyer.[2k] (*c*) Miller.[2l] (*d*) Miller, J. B.: Unpublished data.

The clysis standard to which it is attached is to be found in every hospital. The clysis bottles, needles, and plastic tubing are of the disposable type, ordinarily discarded as rubbish. The large-diameter tube is to be found in most laboratories. The De Vilbiss #40 nebulizer is practically the only piece of equipment which requires a financial outlay, and this is a very inexpensive and widely distributed instrument.

The versatility of the apparatus is based on its ability to nebulize any aqueous therapeutic solution required. It is primarily used for continuous detergent aerosols. When continuous antibiotic therapy is indicated, the antibiotic can be dissolved in the detergent solution contained in the upper bottle (delivery bottle). Penicillin and streptomycin are perfectly compatible with the detergent solution. When it is desired to combine continuous detergent therapy with intermittent antibiotic therapy, the antibiotic can be injected at intervals with a hypodermic needle and syringe into the delivery tube. About thirty minutes before the antibiotic is injected, the delivery tube and the siphon tube are clamped, and the oxygen is allowed to continue to flow, so as to expel the residual detergent solution from the reservoir of the nebulizer. Otherwise the antibiotic solution would be diluted by the detergent and would also be rapidly siphoned off into the collecting bottle. After the antibiotic is nebulized completely, both clamps are opened and the detergent solution resumes flow. The upper clamp is opened first to fill the nebulizer reservoir and adjust the drip rate, then the lower clamp is opened to allow siphoning off of the excess solution, just as when therapy is started. Not only antibiotics but decongestants, such as phenylephrine (neo-synephrine®) hydrochloride, and bronchodilators such as isopropylarterenol (isuprel®) hydrochloride may be administered in this way, so long as attenion is paid to proper dosage.

This apparatus is extremely reliable in continuous therapy. The generation of aerosol never stops so long as the delivery bottle is repeatedly refilled from the collecting bottle or from additional stock bottles. The nebulizer can never fill up and spill solution out onto the patient, as the siphon keeps the solution at a safe and constant level in the nebulizer reservoir. The rubber stopper cannot slip out of the nebulizer, for the two needles bent in opposite directions would catch it and hold it in, so that the patient would continue to receive therapy as usual.

Only two precautions require emphasis: 1. The nebulizer must be handled gently to prevent breakage. It should be taped or clamped to the standard by its neck rather than by its widest portion, for the neck consists of thicker glass. 2. If the capillary side tube within the nebulizer becomes occluded by a piece of soot or lint, it should be blown out by a forceful stream of water from a hypodermic syringe, rather than by probing with needles or other solid objects. The slightest chipping of the capillary side tube may greatly diminish the effective aerosol production of the nebulizer.

SUMMARY

A reliable, versatile, and inexpensive apparatus for prolonged continuous aerosol administration is described. The apparatus is suitable for nebulizing any aqueous solution and has been extensively employed with a special solution for liquefying bronchopulmonary secretions and wetting the respiratory epithelium.

904 Dauphin St.

Obituaries

ANGEL ARTURO ABALLI, M.D.
1880-1952

Dr. Angel Arturo Aballi was born in Matanzas, Cuba, on Sept. 30, 1880. He died July 22, 1952, in the city of Habana. His life has been considered a beautiful example for future generations, and because of his great character he was loved and admired by all who knew him.

Dr. Aballi served as professor of pediatrics at the University of Habana School of Medicine for forty-two years and retired only four years ago. He then was appointed Professor Emeritus. He also served as dean of the Medical School of the University of Habana for several years. The new building was named after him.

He was the founder of the Cuban School of Pediatrics, and was the first president of the Cuban Pediatric Society. He was also recognized as one of the greatest pioneers in the field of medicine in Cuba, and one of the founders of the Cuban Medical Federation.

As a man he was a philosopher, ready to give the best advice to anyone who sought him.

The Medical School has lost one of its greatest members, and his memory will linger in the hearts of his countrymen.

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Society Transactions

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Horace L. Hodes, M.D., *President*

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First Session

Monday, May 5

Icterus Induced in Newborn Mice. Dr. Alex J. Steigman, Louisville.

Isolation of Coxsackie viruses from humans has occasioned an increasing use of suckling mice. We have encountered a previously undescribed phenomenon in such animals. This consists of jaundice without hepatic necrosis, associated with hemolytic anemia and with capillary hemorrhage particularly marked in the central nervous system, following inoculation of baby murine carcass. There is no evidence to suggest that this phenomenon is due either to a virus inoculated or to provocation of a latent murine virus.

Feces of 40 student nurses with a febrile undefined minor illness were studied. No etiologic agent was recovered in mice, suckling mice, embryonated eggs, or monkeys. Equivocal signs in some inoculated suckling mice led in 12 instances to subinoculations tantamount to blind passages at 11 to 12 days after primary inoculation. In 3 of the 12 instances these subinoculations resulted in jaundice, once from the third blind passage and twice from a single blind passage. These three icterogenic pools consisted of the whole-carcass suspensions filtered through sintered glass (UF Corning) filters, which rendered them bacteria-free.

In 36 to 48 hours after subcutaneous inoculation with icterogenic pools, distinct jaundice developed in the recipients; stunting and frequently death ensued. Attempts at passage of the phenomenon by inoculation of the whole jaundiced animals (or livers, brains, or blood separately) did not succeed. Plasma bilirubin pooled from a number of icteric mice was of the order of 7 to 8 mg. per 100 ml. (Evelyn and Malloy method).

A striking feature was the influence of age. Thus, of 275 newborn mice (used within 12 hours of birth), the icterogenic pools produced jaundice in 182 (66%). The incidence fell to 36% at 3 days; mice 4 days and older were resistant.

During the height of jaundice the histologic appearance of the liver was normal for the age. Capillary hemorrhage was noted under the skin and to a very marked degree in the central nervous system. The peripheral blood showed striking degree of polychromatophilia, reticulocytosis, target cells, and spherocytes suggestive of an active hemolytic process.

The phenomenon could not be prevented by prior administration of vitamin K to the mothers or to their offspring at the time of inoculation of the icterogenic pools. A mixture of inoculum with human gamma globulin or with convalescent sera of the original patients failed to prevent jaundice. In order to determine whether bilirubin absorption from the hemorrhages was alone responsible for the phenomenon in presumably immature livers, liters were injected with heparin; marked ecchymoses resulted, but no jaundice ensued.

A small number of animals survived, allowing subsequent histologic studies. After six days of jaundice the liver was seen to have considerable fatty metamorphosis and pigment deposition but no necrosis or inflammatory reaction. After 21 days the striking hemorrhage of the central nervous system was no longer seen, nor was residual gliosis noted.

The absence of hepatic necrosis and the sharp limitation to early neonates are striking. It is postulated that icterogenic pools have a direct effect on erythropoiesis, producing hemolytic anemia, and that they modify the hepatic cell mechanisms for bilirubin transfer in the immature liver.

DISCUSSION

DR. A. ASHLEY WEECH, Cincinnati: May I ask if the van den Bergh reaction was direct?

DR. ALEX J. STEIGMAN, Louisville: Dr. Weech, who has done so much important work on bilirubin economy in the newborn, has asked a question which we should like to answer, but we have been limited technically by the small size of the animals, which weigh approximately 1.5 gm. As an example, it has been impossible as yet to devise satisfactory techniques for serum. Bilirubin concentrations have had to be done on heparinized plasma, a fact which has called for modifications in microtechniques. There are a great many biochemical determinations that we have thus far not been able to do.

Cultivation of Poliomyelitis Virus in Tissue Culture with Particular Reference to the Use of Chemically Defined Media as Nutrient Fluids. DR. A. J. RHODES, DR. A. E. FRANKLIN, DR. W. WOOD, and DR. D. DUNCAN, Toronto, Canada.

In most previously reported studies on the cultivation of poliomyelitis virus in tissue culture, the nutrient fluid used has been Hanks's balanced salt solution, with Simms's ox-serum ultrafiltrate. This nutrient contains no protein and is not particularly well suited to supporting the metabolic activities of the suspended tissue fragments. We have investigated the possibility of replacing Hanks-Simms fluid with a synthetic nutrient fluid known as mixture 199, devised by Morgan, Morton, and Parker.

Most of the experiments reported have been carried out by the Maitland, or so-called "suspended-cell," technique. Human embryonic brain and cord or kidney have been used as the source of tissue. The metabolism of the suspended tissue has been followed by estimating pH and the amount of glucose used. The results can be summarized as follows:

1. Mixture 199 can be used as the source of nutrient for the routine propagation of Lansing virus in flask cultures. It has also proved satisfactory for the propagation of all three types of poliomyelitis virus in roller tubes.

2. Human embryonic brain and cord tissue survives for a considerably longer period in mixture 199 than in Hanks-Simms fluid. This longer survival is accompanied by a prolonged liberation of virus.

3. Kidney tissue also survives for a prolonged period in mixture 199, and virus titers have been substantially higher than in brain and cord cultures.

4. In cultures of brain and cord, tests for glucose utilization give a valuable indication of the state of metabolism of the suspended tissues. Less glucose is used by infected cultures than by control cultures. By contrast, only minimal differences have been observed in glucose utilization in control and infected cultures when kidney is used as the source of tissue.

5. Mixture 199 has also been used in roller-tube cultures of monkey testicular tissue. With this mixture, there is an abundant growth of fibroblasts, and the spaces between the fragments become occupied by cells. Active proliferation of fibroblasts has been noted 75 days after setting up of control cultures. It appears that some proliferation of fibroblasts may also occur in cultures infected with certain strains of virus, even at the same lengthy interval.

DISCUSSION

DR. ALEX J. STEIGMAN, Louisville: I was wondering whether Dr. Rhodes felt that because of the disparity in findings between glucose utilization and pH change, which is the chiefly used end-point indicator, there are independent mechanisms controlling the two observations.

QUESTION: I should like to ask Dr. Rhodes whether the cytopathogenic effect was the same in the presence of mixture 199 as in the presence of the ordinary media. If the cells are destroyed, I should think no more virus would be produced. Possibly mixture 199 supplies something that permits the cells to establish a rather different state of affairs.

DR. ALBERT B. SABIN, Cincinnati: I want to ask Dr. Rhodes first whether he thinks the virus grows in the bit of implanted tissue or in the fibroblasts that grow out from it. Secondly, if you cut out some of the fibroblasts that grow out of the bit of tissue and transplant them, can you maintain continuous growth of those fibroblasts in this medium, and if you can, have you put virus on them?

DR. A. J. RHODES, Toronto, Canada: Some of these questions, as might be anticipated, are rather apt to floor me. We have not yet studied a sufficient number of strains in mixture 199, but it would appear that strains vary considerably in their cytopathogenic effect.

With the Lansing strain and certain other strains studied in our laboratory, there appears to be some sort of agreement reached between the cell and the virus, in that virus growth occurs and some cell degeneration occurs but there is still some cell growth, as though the two processes go on independently.

Dr. Sabin's questions were very much to the point. We have not as yet done anything with these cultures beyond examining them. We have not attempted to cut out cells and subcultivate them. It would be extremely interesting to do this. I believe that possibly one might be able to subcultivate cells and certain virus strains together for a fairly long time, the two managing to get along with each other fairly well.

As to whether the mechanism of glucose utilization was the same as that shown by changes in pH, I would think that it probably is and reflects similar changes in the metabolism of the tissues. However, that is just a guess. We do not have any experimental work to provide a proper answer to that question.

Respiratory Patterns in Newborn Infants as Determined by Air-Flow and Pneumographic Studies and Their Possible Relationship to Pulmonary Hyaline Membranes and Neonatal Mortality. DR. HERBERT C. MILLER and DR. FRANKLIN C. BEHRLE, Kansas City, Kan.

Pneumographic tracings of the movements of the upper chest, lower chest, and abdomen were studied in relation to air flow in and out of the mouth and nose of a large number of newborn infants weighing 1,000 gm. or more at birth and aged up to 50 days. Using a four-channel Sanborn polyviso cardiette, we found that the respiratory pattern immediately after birth consisted in the simultaneous expansion and contraction of all parts of the chest and abdomen. In older and more mature infants this pattern was modified to the extent that as the abdomen expanded the lower part of the chest and sometimes the whole chest was contracted, suggesting that the thoracic muscles were playing a negligible or even completely negative role in the exchange of gases. Attempts were made to quantitate the relative roles of the diaphragm and the thoracic muscles in the exchange of air, a Marey capsule connected to pneumographic tubes placed about the chest and abdomen being used. These studies confirmed the previous ones and indicated that with increasing age and maturity the diaphragm played an increasing role and the thoracic muscles a decreasing role in air exchange. By 5 days of age it appeared that most respiration was being carried out by the diaphragm.

Newborn infants in respiratory distress who died in the first 48 hours of life were closely observed in respect to their pattern of breathing. It was noted that these infants were making more vigorous efforts to breathe with the chest than with the diaphragm. The latter appeared to be playing a negligible role in air exchange. Such infants were found to have hyaline membranes in their lungs.

It was postulated that insufficient "vagal tone" might account for the diminished activity of the diaphragm in the infants who died, since in animal experiments the motor discharges of the phrenic nerves are directly related to vagal afferent stimuli produced by stretching the lung.

DISCUSSION

QUESTION: I should like to know whether Dr. Miller has any patterns for infants who did not have hyaline membrane pneumonia or hyaline membrane lungs but who had respiratory distress in this period.

DR. WALDO E. NELSON, Philadelphia: I should like to modify the question asked to this extent: Has Dr. Miller observed the findings described in infants who did not have any evidence at postmortem examination of intrapulmonary hyaline membrane but who did have a widespread interstitial pneumonitis or bronchiolitis?

DR. HORACE L. HODES, New York: I want to raise one point. It seems to me that the objection to experiments of this type has been on the basis that if vagotomy is done in rabbits and care is taken to provide an adequate airway, such effects as pulmonary edema do not occur. Can you say anything about this point?

DR. HERBERT C. MILLER, Kansas City, Kan.: We have not had the opportunity to get respiratory patterns either with the polyviso machine or with the kymograph for babies who have died from causes other than hyaline membrane disease. So far, the few babies who have died after tracings were made have been found to have had hyaline membrane disease, which is not too unexpected, considering the high incidence with which these membranes are found in neonatal pathology.

As to Dr. Hodes's question, people have been doing vagotomies on animals for 2,000 years. The physiologists still argue as to what vagotomy does to the animal. There are at least three separate theories. Animals that have had a tracheotomy in addition to the vagotomy seem to do better than those which are not tracheotomized. This fact has led to the theory that obstruction has something to do with the changes that are seen in the lungs of the vagotomized animal.

The fact remains that even among tracheotomized animals, one can see certain changes in the lungs, consisting in pulmonary edema, and we have seen hyaline membranes in the lungs of animals in spite of the fact that they have had tracheotomies.

Preliminary Studies of Liver Glucose-6-Phosphatase in von Gierke's Disease. DR. RUTH C. HARRIS, New York.

In 1939 the Coreys postulated that conversion of glycogen to glucose in liver results from action of (1) a phosphorylase which catalyzes hydrolysis of glycogen to glucose-1-phosphate, (2) a phosphoglucomutase which converts glucose-1-phosphate to glucose-6-phosphate, and (3) a phosphatase which splits the latter to glucose. After this theory was put forward Tannhauser showed that alkaline phosphatase in the liver is decreased in patients with glycogen-storage disease. Since that time the defect in von Gierke's disease has been thought to result either from an abnormal glycogen molecule or from the absence of phosphorylase, glucosidase, phosphoglucomutase, glucose-6-phosphatase, or a combination of such abnormalities.

When pure glucose-6-phosphate was used as the substrate, the liver glucose-6-phosphatase of two patients with clinical and histological evidence of von Gierke's disease was very low when compared with that of liver biopsy specimens of children of corresponding age. The values for phosphatase activity were expressed as the milligrams of inorganic phosphorus liberated from the substrate after incubation at 37 C. for 30 minutes. The results in the control group ranged from 1.9 to 5.6 mg. of phosphorus per gram of wet weight of liver. The control specimens were from infants and children with poor nutrition but with no obvious liver disease.

Livers from two patients, aged 5 months and 10 years, with proved von Gierke's disease yielded phosphatase values of 0.1 to 0.23 mg. of phosphorus per gram of wet weight. These results are considerably lower than those for any other disease tested. Of interest is the fact that a functioning, invasive hepatic-cell tumor found in the 10-year-old child contained larger amounts of glycogen than the more normal liver and exhibited slightly less phosphatase activity. Tests on this liver for study of the existence of an inhibiting factor showed no evidence that such a factor was present.

Values obtained in four other types of liver disease ranged from 0.65 to 4.21 mg. of phosphorus per gram of wet weight of liver. The highest values were obtained in cases of bile-duct obstruction and the lowest values in severe cirrhosis. One infant with biliary cirrhosis accompanied by suggestive histological evidence of increased liver glycogen deposition had a liver phosphatase value of 0.67 mg. of phosphorus per gram.

It is suggested that this test be used as a part of the routine diagnostic study of von Gierke's disease.

DISCUSSION

DR. GILBERT B. FORBES, Dallas, Texas: Apropos of Dr. Harris' remarks concerning two patients Dr. Corey presented at New York City a few weeks ago, I had an opportunity to see one of those patients and should like to tell you a little bit about the case because it throws additional light on the fact that von Gierke's disease as seen clinically may be of varied etiology.

The patient was a 12-year-old girl in relatively good health who showed many of the criteria applied clinically for von Gierke's disease, except as to age and as to apparent prognosis, which was better than that of most patients. The specific liver phosphatase was obtained at biopsy, and the samples were frozen with solid carbon dioxide immediately and flown to St. Louis.

The specific phosphatase was low but by no means absent. The major effect which Dr. Corey postulated was yet another enzyme which has to do with the glycogen.

[Slide] Glycogen is apparently made up in a form which resembles a branching tree, with straight chain linkages in the 1-4 position and occasional side-branches in which the linkage is in the 1-4 position.

The phosphorylase which Dr. Harris talked about is apparently active only in the 1-4 position, and when the molecule is degraded to a branch point, another enzyme must act before more glucose can be liberated. This enzyme acts only at branch point and has been given the name of amylo-1-6-glucosidase. It may be responsible for the patient's relatively good prognosis and for the mildness of her disease.

DR. L. EMMETT HOLT JR., New York: Two or three years ago we had an opportunity to make measurements of glucose-6-phosphatase on a specimen of liver obtained at biopsy from a patient with von Gierke's disease. The measurements were made by Dr. Spurtes, a member of Dr. Ochoa's staff. Like Dr. Harris we found that the concentration of enzyme per gram of liver was strikingly reduced. We were happy about this finding until we realized that in relating the concentration of enzyme to a unit of liver weight we had failed to take into consideration the fact that owing to the enormous distention of the liver cells a given weight of liver contains only a fraction of the number of cells that would be contained in a gram of normal or of noninfiltrated liver. Until some one has shown that the glucose-6-phosphatase per liver cell or per gram of liver nitrogen is reduced I am afraid we are not justified in concluding that a defect of this enzyme is responsible for von Gierke's disease.

Hemagglutinins of the St. Louis and Western Equine Encephalitis Viruses: Isolation, Properties, and Use for Diagnosis and Epidemiologic Survey. DR. ROBERT M. CHANOCK and DR. ALBERT B. SABIN, Cincinnati.

Specific hemagglutinins for chick erythrocytes were recovered from recently isolated strains of St. Louis (SLE) and western equine (WEE) encephalitis viruses, but not from strains with many passages in mice. WEE- and SLE-infected mouse brain ground as a 20% suspension in 0.016 M borate potassium chloride solution at pH 9.0 and centrifuged at 2,000 rpm for 10 minutes or 13,000 rpm for 1 hour served as the source of hemagglutinin. WEE hemagglutinin was no longer demonstrable after freshly isolated WEE virus had undergone more than six consecutive intracerebral mouse passages, whereas SLE hemagglutinin was still present at the 23d mouse passage (the highest passage tested). Each hemagglutinin has its own specific pH range for reaction with the chick red cell: fresh SLE hemagglutinin at pH 6.6 to 7.1 (optimum 6.6 to 6.9) and WEE hemagglutinin at pH 6.0 to 6.3 (optimum 6.1 to 6.2). The use of an alkaline buffer (pH 9.0) for extraction was important for the successful isolation of the hemagglutinins.

No receptor-destroying enzyme was associated with either hemagglutinin. While the receptors for both hemagglutinins were uniformely present on the erythrocytes of newly hatched chicks, they occurred irregularly or not at all on the erythrocytes of adult chickens.

Reproducible hemagglutination-inhibition tests could not be carried out until it was realized that both hemagglutinins were rapidly destroyed in the free state at the pH for reaction with the chick erythrocyte. This difficulty was overcome by diluting the hemagglutinin at a more alkaline pH, at which it was stable, and the serum at a more acid pH, so that the resulting pH after mixture was that optimum for hemagglutination.

All human sera contain a normal inhibitor for both hemagglutinins in high enough concentration to prevent the determination of specific hemagglutination-inhibition antibody. These inhibitors (which appear to be lipid or lipoprotein) can be removed from the serum by acetone precipitation and extraction, which leaves the specific hemagglutination-inhibition antibody unaltered in the precipitated protein fraction.

Hemagglutination-inhibition tests with the acetone-treated acute and convalescent sera of seven patients with western equine encephalitis and eight patients with St. Louis encephalitis yielded distinct and specific diagnostic results. In addition, a presumptive diagnosis could be made earlier than by the complement-fixation test, since the hemagglutination-inhibition antibodies were present in moderate to high titer early in the course of the disease. In a limited number of tests, the hemagglutination-inhibition technique has equaled the sensitivity and accuracy of the neutralization test in detecting past inapparent infections with SLE virus.

DISCUSSION

DR. ALFRED L. FLORMAN, New York: I have two questions. First, is there any evidence to correlate infectivity and hemagglutinin ability or, rather, is there any relationship between the hemagglutinin and the virus particle? Second, is there any evidence that the extraction processes used remove only the nonspecific inhibitor and none of the specific inhibitor?

DR. ROBERT M. CHANOCK, Cincinnati: Dr. Florman's second question is the easier one to answer. The question was whether the inhibitor is completely removed from the serum by acetone treatment; also, whether there was any effect on specific antibody.

There is no effect of the acetone treatment on the specific antibody. The antibody titer remains unchanged in the acetone-precipitation fraction.

The inhibitor is removed to the extent that sera which originally inhibited 8 to 16 units of hemagglutinin in very high dilutions failed to inhibit in very low dilutions in tests with the acetone-precipitated fractions. There may still be some left, but by the test we used it is possible to show that at least 99% of the hemagglutinin inhibitor can be removed.

With regard to the other question, we cannot say what the relationship is of hemagglutinin to infective particle at the present time.

Measurement of Glomerular Filtration Rate in Children with Kidney Disease. DR. GUILHERME MATTAR (by invitation), DR. HENRY L. BARNETT, DR. HELEN MCNAMARA (by invitation), and DR. HENRY D. LAUSON (by invitation), New York.

Estimation of glomerular filtration rate in patients with kidney disease provides an important means of judging extent of kidney impairment and therefore progress of the disease. In addition, this measurement is basic to many important observations on renal-tube function. The clearance of inulin is generally accepted as a measure of this rate in normal subjects. If the clearance of an endogenous substance also measured glomerular filtration rate in both normal children and children with kidney disease, clearance studies would be greatly simplified.

With specific methods (Hare) for measuring endogenous creatinine in serum and urine, the mean creatinine : inulin clearance ratios in 24 infants and 12 children with normal kidney function were 1.00 and 1.03, respectively. However, the endogenous-creatinine : inulin ratios were consistently elevated in children with reduced kidney function. The thiosulfate : inulin clearance ratios in these children showed the same range of values at all levels of inulin clearance and centered about unity. These data suggest that clearances of inulin and thiosulfate rather than of creatinine measure the glomerular filtration rate in children with reduced kidney function.

In two children with reduced kidney function who had high creatinine : inulin ratios, the relation of rate of excretion of inulin to concentration of inulin in plasma was expressed by a straight line extrapolating to zero coordinate, providing further evidence that inulin is measuring glomerular filtration rate in these children.

Assuming that inulin does measure this rate in children with kidney disease and consequently that creatinine is secreted by the tubules, we attempted to reduce the high creatinine : inulin ratios in these children by substances which inhibit tubular secretion. Comparison of creatinine : inulin ratios at low and high concentration of *p*-aminohippurate revealed a slight increase in four of five observations. However, high concentrations of *p*-aminohippurate were found to interfere with the chemical determination of creatinine when Lloyd's reagent was used. It appears, however, that high concentrations of *p*-aminohippurate do not depress the ratio.

Carinamide is known to inhibit tubular secretion of penicillin, *p*-aminohippurate, iodopyracet injection (diodrast®), and phenolsulfonphthalein (phenol red). One single large dose of carinamide reduced the *p*-aminohippurate clearance to the inulin-clearance value and well below the simultaneously determined creatinine clearance. This observation strongly supports the conclusion that inulin rather than creatinine is measuring the glomerular filtration rate. When given over a period of two days, carinamide did depress the creatinine : inulin as well as the *p*-aminohippurate : inulin clearance ratios close to 1.

Desoxycorticosterone glucoside is known to depress tubular reabsorption of glucose, and if complete inhibition occurs the clearance of glucose should reach the level of the glomerular filtration rate. However, with 100 mg. given intravenously, only 60% inhibition of tubular reabsorption was obtained in a normal child and considerably less in two children with reduced kidney function.

It is concluded (1) that the clearance of inulin does measure the glomerular filtration rate in children with kidney disease, and consequently the high creatinine : inulin ratio is explained by tubular secretion of endogenous creatinine in these patients, and (2) that endogenous-creatinine clearances may measure glomerular filtration rate in normal infants and children but not in children with kidney disease.

DISCUSSION

DR. MILTON RAPOPORT, Philadelphia: I think that Dr. Mattar and his co-workers have apparently found a useful absolute measurement of glomerular filtration rate. If it is valid, it is a simple and useful method and takes measurement of glomerular filtration rate out of the laboratory and moves it into clinical practice. It is a real contribution.

DR. SOLOMON A. KAPLAN, Cincinnati: I should like to ask a question about the thiosulfate clearances. Recently it has been shown by Luetscher and by Foulks and associates that thiosulfate is actively transported by the renal tubules and that injection of testosterone or cortisone into female dogs increases the rate of tubular transport. In male dogs thiosulfate clearance ordinarily exceeds the filtration rate. Would the authors state whether the discrepancies they found in clearances of thiosulfate were greater in boys than in girls?

DR. GUILHERME MATTAR, New York: I was not aware of the work on thiosulfate transport by tubules. However, the thiosulfate : inulin ratios were close to 1 in our cases. I should like to ask Dr. Barnett to clarify this point.

DR. HENRY L. BARNETT, New York: There is unquestionable evidence from various sources that the clearance of thiosulfate does not provide a good measure of glomerular filtration rate, and I think that part of the variation observed in these children was probably due to varying degrees of reabsorption or secretion. This fact does not, however, invalidate conclusions drawn from the data on simultaneous thiosulfate and inulin clearances. If they were not both at the level of glomerular filtration, one would have to conclude that the net result of tubular transport was the same for the two, which is unlikely. In regard to the sex difference in the handling of thiosulfate, our children were all under puberty and I do not think we should expect to see any sex difference.

Role of Ascorbic Acid in the Function of the Adrenal Cortex. DR. CHARLES T. STEWART (by invitation), DR. ROBERT J. SALMON (by invitation), and DR. CHARLES D. MAY, Minneapolis.

Attention has been focused on the role of ascorbic acid in the function of the adrenal cortex because of the high concentration of this vitamin in the adrenal gland and its depletion upon administration of corticotropin. If an abundance of ascorbic acid were essential for normal functioning of the adrenal cortex, one might anticipate an impairment of adrenocortical function in scurvy.

An investigation of the functional capacity of the adrenal cortex was undertaken in monkeys rendered deficient in ascorbic acid. The evidence selected as means of detecting alterations in the functional capacity of the adrenal cortex was the level of eosinophiles in the peripheral

blood, the effect of intravenously injected insulin on the level of glucose in the blood, and the urinary excretion of 17-ketosteroids before and during administration of corticotropin.

The level of circulating eosinophiles gradually declined during the deprivation of ascorbic acid and upon the advent of gross scurvy was usually zero, suggesting increased adrenocortical activity. As an adrenalectomized monkey showed marked eosinopenia during the "stress" of an infection, the depression of eosinophiles in the scorbutic monkey was considered inconclusive evidence of increased activity of the adrenal cortex.

It was of considerable interest to find that the response to insulin in scorbutic monkeys was of a type also suggesting an increase in the production of adrenocortical hormones. The level of glucose in the blood was never more than slightly depressed by insulin and frequently actually rose. Control animals treated with cortisone exhibited a response to insulin like that in scurvy. Data indicated that the action of insulin in scurvy is not enhanced by the simultaneous administration of ascorbic acid, folic acid, or reduced glutathione.

In monkeys deprived of ascorbic acid for 30 days, the spontaneous urinary excretion of 17-ketosteroids was significantly lower than in control animals. The onset of gross scurvy was accompanied by a suggestive rise in the spontaneous excretion of 17-ketosteroids toward the control level. Even after 100 days without ascorbic acid, monkeys with severe scurvy of 20 days' duration exhibited as great a rise in the urinary excretion of 17-ketosteroids during the corticotropin administration as did control animals.

The liver and adrenal content of ascorbic acid declined markedly during the first 30 days without ascorbic acid, but little further reduction occurred even after 100 days of deprivation.

The effects of scurvy were similar to those of "stress" produced by sterile turpentine abscesses: eosinopenia, only slight depression of blood glucose by insulin, and a rise in the spontaneous urinary excretion of 17-ketosteroids.

These data indicate that in scurvy, which may act as a form of "stress," the adrenal cortex is still able to respond by producing hormones normally in spite of severe deprivation of ascorbic acid. None of the scorbutic monkeys, some with severe scurvy of 20 days' duration, failed to produce normal urinary excretion of 17-ketosteroids upon stimulation with corticotropin. A terminal exhaustion of the adrenal cortex may eventually occur, but none of the animals reached such a stage in these experiments.

DISCUSSION

DR. CHARLES D. MAY, Minneapolis: The main thing, I think, is simply to reemphasize the interesting fact that in severe deprivation of ascorbic acid the adrenal gland puts out hormones in a normal fashion. This is not to say that a very marked decline which occurs in assimilation of corticotropin in conjunction with the hormones under normal circumstances may not have some significance. It perhaps points up a more peculiar significance comparable to that which the adrenal corticotropin has upon circulating eosinophiles.

DR. HAROLD E. HARRISON, Baltimore: Recent studies have shown that ascorbic acid under in vitro conditions can form part of a system for introduction of hydroxyl groups into aromatic rings and also steroid rings. This physiological mechanism might conceivably be of importance, since some of the potent adrenal corticosteroids do have hydroxyl groups.

It might be of interest to see whether the type of steroid put out by the adrenal cortex deficient in ascorbic acid is physiologically active but chemically different from normal corticosteroids. This possibility seems rather unlikely, but it would be worth pursuing the subject to see whether in the absence of ascorbic acid steroids with hydroxyl group substitutions could be elaborated.

DR. SHEPPARD, Rochester, Minn.: I want to ask if any liver function tests were done on these monkeys. Possibly the liver was unable to handle the steroids.

DR. CHARLES D. MAY, Minneapolis: Liver function tests were not done in this experiment, but we have studied liver function in scorbutic animals and have carried out histological examinations, and we have not found any evidence of impaired hepatic function.

I am responsible for not having measured the 11-oxy-corticosteroids, for which the methods are more involved. This experiment was set up in an effort to utilize a few remaining months before Dr. Stewart enlisted in the Air Corps, and so we chose to take a rapid approach to information which would indicate the general state of affairs.

We chose the 17-ketosteroids as being a reliable index of response to adrenocorticotropin.

A paper recently appeared in England indicating that there is a spontaneous rise in 11-oxy-corticosteroids in scurvy, in which case the gland is able to elaborate both 17-ketosteroids and 11-oxy-corticosteroids.

Serum Gamma Globulin Levels in Infancy. Dr. O. Orlandini T., Dr. A. Sass-Kortsak, and Dr. J. H. Ebbs, Toronto, Canada.

A knowledge of the values of serum gamma globulin in normal infants was thought to be of value in view of the increasing interest in this subject.

The subjects of study were 28 normal mothers at the time of childbirth, their 28 newborn infants (cord blood), another 122 normal infants, and 13 young adult women for comparison. Gamma globulin was determined with the salt-precipitation method of Jager and Nickerson. In the same sera total protein and albumin were determined. Methods were chosen which had been shown by others to give reasonably good agreement with electrophoresis.

The mean gamma globulin level in newborn infants was slightly higher than in the mothers, but the difference was found to be statistically insignificant. The values for both mothers and newborn infants corresponded to those of normal adults. In the first month of life gamma globulin levels decreased to about one-third the value found at birth. Until 3 months of age there was no further change, after which there was a slow rise. At 2 years of age adult values are closely approximated but not yet reached.

When the logarithms of the values in the first four weeks of life were plotted against age they were found to be close to a straight line. This would mean that the correlation between serum gamma globulin concentration and age in the first four weeks of life shows the characteristics of simple exponential decay. A hypothetical explanation of this finding was attempted.

Absence of Serum Gamma Globulins. Colonel Ogden C. Bruton, Medical Corps, United States Army, Dr. Leonard Apt, Dr. David Gitlin, and Dr. Charles A. Janeway, Boston.

We wish to present an entity, not previously described, that is characterized by recurrent severe bacterial infection associated with almost complete absence of serum gamma globulins but with normal total protein concentration.

Three boys, each now about 9 years of age, have had multiple infections since infancy or early childhood. The illnesses have included pyoderma, purulent conjunctivitis, otitis media, purulent sinusitis, pneumonia, meningitis, acute arthritis, and sepsis—often with bacteremia. The prominent organisms encountered have been Pneumococcus, Staphylococcus aureus, Hemophilus influenzae, and Meningococcus. Although the infections have been severe and the patients often critically ill, they have usually responded promptly to antibiotic and sulfonamide therapy.

The children appear to be normal in all other respects. Physical examination has been remarkable for the absence of abnormal findings except those associated with the acute illness. In spite of their many infections the boys are above average in nutritional and physical development. There has been no clinical or laboratory evidence of disease of the major organ systems.

One boy had sepsis 18 times, with eight types of pneumococci obtained on blood culture on 10 different occasions. Sulfadiazine (1.0 gm. a day) for two years apparently did not prevent infections. A series of injections of pneumococcal antigens, in the form of autogenous vaccine, prepared vaccine, and polysaccharide did not control infections. Antipneumococcus antibody could not be demonstrated in the patient's serum. The Schick test was positive after a series

of injections of diphtheria toxoid and four booster injections. There were no typhoid antibodies after the administration of typhoid vaccine. The complement-fixation test for mumps was negative three weeks after a typical attack.

Electrophoretic analysis of the serum revealed the absence of gamma globulins, but the total protein, albumin, and globulin concentrations obtained by routine salt fractionation methods were within normal limits.

The boy has been given 3.2 gm. of human gamma globulin intramuscularly at monthly intervals, with no other prophylactic measures, for 14 months and has had no further attacks of sepsis.

Although the other two boys have had the same types of illnesses, recurrent pyoderma, sinusitis, pneumonia, and pyogenic arthritis have been more conspicuous. One had H. influenzae meningitis; the other, meningococcal and pneumococcal meningitis. Penicillin, 100,000 to 200,000 units given orally each day for four years, was without apparent benefit, but broad-spectrum antibiotics in moderate doses and aerosol therapy have greatly reduced the number of infections.

Specific antibodies were not demonstrable in the serum after a series of injections of diphtheria, pertussis, and tetanus toxoid; pneumococcal polysaccharide, and influenza virus A and B vaccines. Gamma globulin was absent in the electrophoretic analysis of the serum of both boys, but minute amounts could be detected by immunochemical methods. The total protein, albumin, and globulin concentrations measured by the routine method were normal.

Examination of the sera of the siblings, parents, and one set of grandparents of the later two boys revealed normal amounts of gamma globulin.

The third child was given human gamma globulin in the form of hyperimmune plasma on two occasions and the rate of disappearance of gamma globulin studied immunochemically. This was checked by simultaneous measurements of the levels of transfused antibodies. The "half life" was 20 days or longer.

It is postulated that these children have a congenital defect of the plasma proteins analogous to hemophilia or afibrinogenemia. The entity has probably not been recognized previously because specific methods for the detection of serum gamma globulins were lacking and because the severe infections contracted by such children were usually fatal prior to the era of chemotherapy.

DISCUSSION

DR. BELA SCHICK, New York: Dr. Apt mentioned that cases have been published of low gamma globulin, but the patients had edema and the total protein was low. One such case was published by Dr. Greenbaum and myself. It was interesting that the child had edema from birth and the mother also had some tendency to edema.

The patient is now 20 years old, and is perfectly normal except for persistent edema, which changes from time to time in intensity. The tendency toward edema lessened after puberty. The important findings in this case consist of low total serum protein and almost complete absence of gamma globulin. Contrary to the teaching that gamma globulin as carrier of antibodies guarantees better immunity, our patient, with very little gamma globulin, is never sick and never missed a school day except on account of measles or chicken pox, diseases which have nothing to do with general immunity. She has intensive edema and sometimes fluid in the abdomen. She suffers psychologically. She has so-called "piano legs" and is therefore reluctant to go swimming or dancing. She is actually a very good-looking and intelligent person.

In a similar case published by McQuarrie, a child with edema died at 3½ years of age after having an ear infection complicated by mastoiditis and sepsis. At autopsy a congenital defect in the liver was found. No inflammatory signs were detected. This case led to the theory that the liver cannot replace the daily loss of protein and gamma globulin. We accepted this theory for our patient. Her unexpectedly good immunity can be explained by differentiating between humoral immunity, represented by the presence of antibodies in the gamma globulin, and

cellular immunity, based on the potential ability to reproduce antibodies quickly in the absence of gamma globulin.

DR. WALLACE W. MCCRORY, Philadelphia: This is a "me too" comment. We have one patient in Philadelphia who has had nine attacks of meningitis due to various bacteria. This child has had a gamma globulin measurement done by the Kunkle method, which is certainly not to be compared with electrophoresis. We hope to have that later. This case would fit beautifully into the category of the cases described. The determination done showed practically no gamma globulin.

DR. ALFRED L. FLORMAN, New York: I want to comment on the first of the two papers, the paper of Dr. Orlandini and Dr. Sass-Kortsak, which I think is very interesting. Dr. Karelitz and I have been concerned with a particular antibody, the mumps complement-fixing antibody, which is transmitted from mother to child almost in titer. We have observed a number of children and have bled them at serial intervals and made determinations of the complement-fixing antibody levels.

We have not studied enough cases to come to any conclusion as to what the average half life of this antibody would be. I can tell you, though, that while there is considerable variation, by the 12th week after birth none of our patients showed any detectable antibody.

DR. STEWART H. CLIFFORD, Brookline, Mass.: Have they had an opportunity to study the levels in the two extremes of prematurity and postmaturity?

DR. HARRY H. GORDON, Baltimore: My question is directed to the Toronto group. Have they had an opportunity to compare the levels in breast-fed with those in artificially fed infants?

DR. L. NELLES SILVERTHORNE, Toronto, Canada: I was much interested in the last paper. I wonder whether studies have been done on the levels of gamma globulins in patients who have had poor responses to antigens, as well as in adults and children who have had multiple infections.

This year we had just such a patient at the Hospital for Sick Children at Toronto, Canada, a child who has had one pyodermic infection after another, many times receiving antibiotics for many months and many times not receiving these drugs, and yet doing very well.

Historically speaking, I do not believe that children necessarily died in the past because they had prolonged and repeated infections. Older clinicians can tell of many who survived and kept on having infections, and who nevertheless gained and grew. This subject has developed an interesting tool, shall we say, for study of a limited field of immunology.

DR. SAMUEL KARELITZ, New York: I want to ask two questions. First, did any of these children fail to have measles after adequate exposure? Second, were any mumps-antibody determinations made other than measurement of the type and amount of globulin? I noticed that one child had mumps three times.

DR. EDWARD L. PRATT, New York: We have been studying the electrophoretic patterns in 27 premature infants ranging in age from newborn to 65 days, the majority of whom weighed under 1,600 gm. at birth. I do not need to have slides in my pocket, because those you have seen would exactly duplicate ours. The average titer of gamma globulin at birth was the same. The titer decreased to one-half in about 21 days. There was also a decrease in the concentration of albumin during the first five weeks. However, we do not find any particular trend with age in the concentrations of the alpha 1, alpha 2, or beta globulins.

DR. ALFRED H. WASHBURN, Denver: My question is specifically for the authors of the first of these two papers. I am curious to know the socioeconomic status of their group of infants. My reasons is that I am skeptical about comparing infants of poor environment with those of privileged environment—in setting up normal standards it is important to know about the environment.

We have been interested in the plasma globulins for some years. We started out with a group of more or less chance cases from the hospital wards and outpatient departments and

from a couple of orphan homes. Later we studied the globulins in our own group of subjects in the Child Research Council, whose economic and general environmental status is considerably more privileged. We are interested to see that our own group does not reach anywhere near the adult level in two years, as I take it this group did, whereas the first miscellaneous group did get to the adult level at the end of two years.

And then, if I may just make a comment or two, I think it is important that we should not forget that, just as there are patients without globulin, so too among the general run of patients seen in private practice—who make up the same kind of group we are studying in the Child Research Council—there is a tremendous range, some youngsters having remarkably low globulin and some having remarkably high gamma globulin. We are in the process of trying to get some order into that picture.

For example, there are some nice relationships between the amount of lymph tissue and the level of gamma globulin. I think that if you will be patient with us for another few years, while we are studying these youngsters a little farther along in their development, we will be able to give you some of the answers—such as, for instance, the relationships between infections and gamma globulin levels.

Dr. Lytt Gardner, Baltimore: I should like to suggest to the authors one other thing to do if they have not done it. Taking the comment on the condition that was seen in the two siblings together with the observation that the parents of these children do not have depressed gamma globulin suggests that we might be dealing with a simple Mendelian recessive trait.

I would suggest for the future benefit of human geneticists that the authors obtain all available blood groups for both parents, the normal siblings, and the affected children, and that they do phenylthiourea taste tests on these persons and record the information, which may not become valuable until a larger series is obtained.

Dr. A. Sass-Kortsak, Toronto, Canada: As to Dr. Clifford's question, our work in this respect is in progress now.

As far as Dr. Gordon's question is concerned, as you may recall, we had 18 newborn infants whom we were able to follow from birth until 1 week of age; that is, we got the serum gamma globulin level at the time of birth from the cord blood and we got it at 1 week of age. Of these 18, 5 were artificially fed and 13 were breast-fed. These two groups behaved exactly the same way, showing the fastest decrease of gamma globulin levels in the first week of life. It seems, therefore, that the ingestion of colostrum does not contribute a significant amount to the human-serum gamma globulin.

As to Dr. Washburn's question in regard to the social status of the patients we were studying, about half these patients were brought to the hospital for examination before adoption; obviously they had poor social status. The other half were hospitalized for correction of minor surgical conditions; this group included various social classes. We could not see a difference between these two groups, but we did not study this question particularly. In the future we are going to pay more attention to it.

Dr. David Gitlin, Boston: There have been so many questions we cannot hope to answer them all adequately. I should like to emphasize that the immunochemical procedures performed in these experiments were not determinations of titers but quantitative procedures elaborated by Heidelberger and his colleagues. With regard to their relationship to gravimetric determinations, therefore, these procedures are based upon actual amounts of gamma globulin and the values then expressed in relative terms on the charts presented. To use this method, we had to demonstrate that the gamma globulin present in the blood 15 minutes after intravenous administration was the same gamma globulin immunochemically that was present in each blood sample taken over the course of the study.

I wish to state that we determined the half life of gamma globulin not only by estimations of total gamma globulin but also by simultaneous measurements of specific antibodies, anti-B isoagglutinin in one instance and anti-pertussis agglutinin in another. We were able to show that the fall in specific antibody with time corresponded to the fall in total gamma globulin,

thereby eliminating the possibility that the patients were synthesizing gamma globulin during the investigation. On the basis of a half life of gamma globulin of 20 to 30 days in the cases presented, we ascribed the fundamental defect in these cases to an inability to synthesize adequate amounts of antibody. The previous paper gave the half life of gamma globulin as three to four weeks in infants, and this corroborates similar data obtained by other means. Dixon studied the half life of radioactive iodinated gamma globulin in older patients and found it to be about 10 days; he found that in younger children, however, the half life was longer. With regard to London's data on the half life of gamma globulin as being 20 days, we must remember that he used N^{15}-labeled aminoacetic acid, that aminoacetic acid reenters the metabolic pool and then is resynthesized into plasma protein; the half life that London found is really a maximum half life. If we can apply a correction derived from Sterling's data on the half life of albumin, London's data would indicate a half life of gamma globulin of about 10 days. It was for these reasons that Dr. Apt mentioned the possibility of some slight defect in the catabolism of gamma globulin, but obviously more work is required.

We wish to thank Dr. Schick for his comments about low gamma globulin levels or absence of gamma globulin in certain children with edema and the significant absence of infection in these children. The only comment that we might make is that the level of specific gamma globulin may be one of the deciding factors. The fact that electrophoresis shows little gamma globulin is extremely important but is not the whole answer, and the reason is that ordinarily electrophoresis is not accurate in revealing small amounts of protein. We have several patients who have practically no gamma globulin on electrophoresis who have edema and are following the course described by Dr. Schick. These patients do have gamma globulin on immunochemical analysis; they have a level of 100 to 200 mg. per 100 ml. We have found that in the patients described today a total gamma globulin level of 100 to 150 mg. per 100 ml. appeared to prevent infection, but it must be recognized that this gamma globulin was derived from pooled blood and hence contained a great variety of specific antibodies.

We want to thank Dr. Gardner for his comments about the possibility of this syndrome's being the result of a recessive characteristic. We have tested many other patients with severe infections. To date all these patients except one have had normal amounts of circulating gamma globulin; the exception was an adult who had no demonstrable circulating gamma globulin electrophoretically or immunochemically.

DR. LEONARD APT, Boston: A question was asked in regard to the leucocyte response during the infections. A polymorphonuclear leucocytosis developed during most of the illnesses. A leucopenia was noted on only one occasion. The second patient, when first seen at the age of 13 months with staphylococcal septicemia, had a total leucocyte count of 2,500 per cubic millimeter, with no granulocytes. The granulocytes reappeared in the peripheral blood within 24 hours after therapy was begun. Preliminary studies of phagocytic activity of the leucocytes in vitro suggest that this function is normal.

In answer to Dr. Karelitz' first question, concerning multiple episodes of measles after exposures, the first and second patients each had one episode of measles. Although there were no known intimate exposures to other children with measles subsequently, there were children with measles in the community and at school and neither child had a second attack.

In regard to mumps, the first patient supposedly had three attacks. Only the last episode, however, was seen by one of the authors. There was a definite intimate exposure and the illness was typical. The complement-fixation test and skin test were negative. The second boy had only one attack of mumps. The skin tests remained negative and hemagglutinating antibodies were never demonstrable even 10 days after the mumps skin test.

Other antibodies have been found to be absent. One boy, blood group type O, and another, type A, have neither alpha nor beta hemagglutinins in their sera.

We have not had the opportunity to study the gamma globulin levels in patients who have shown a poor response to antigens.

SECOND SESSION
TUESDAY, MAY 6

Demonstration of Type-Specific Streptococcal Antibody by a Hemagglutination Technique Employing Tannic Acid. DR. FLOYD W. DENNY JR., and DR. LEWIS THOMAS, Minneapolis.

Various antibodies have been demonstrated by the technique of adsorbing antigen on sheep erythrocytes and observing agglutination of the cells by specific antibody. Attempts were made to detect antibody against the type-specific M-antigen of Group A streptococci by employing erythrocytes exposed to solutions of this antigen. It was not possible to bring about adsorption of M-protein on the surface of untreated sheep or human red cells.

It is known that when red cells are treated with tannic acid, the adsorption of various proteins to the cell surface is greatly enhanced. Boyden showed that the sensitivity of the Middlebrook-Dubos hemagglutination reaction was much increased when tubercle bacillus antigen was adsorbed to erythrocytes treated with tannic acid.

With similar techniques, M-protein was readily adsorbed on group O human cells, and specific agglutination of such cells was produced by anti-M rabbit sera in dilutions as high as 1:10,000. The development of type-specific agglutinating antibody was also demonstrated in sera from patients with known streptococcal infections. Nonspecific agglutination did not occur with rabbit anti-M sera but was encountered in some samples of human serum with certain types of M-protein.

The hemagglutination test could be converted to one involving hemolysis by the addition of guinea-pig complement to the mixtures of M-sensitized cells and antiserum.

DISCUSSION

DR. ALBERT B. SABIN, Cincinnati: M-substance reacts with antibody; it gives rise to a precipitin reaction, and it presumably should also fix complement. It would be of interest to know what the titers are when those direct methods of antibody demonstration are used, as compared with the indirect method when the antigen is adsorbed on the red cells.

DR. EDWARD C. CURNEN, New Haven, Conn.: Dr. Denny and Dr. Thomas are to be congratulated for this development in a field where new techniques are badly needed. Dr. Rothbard showed that type-specific antibodies against streptococci can be demonstrated, but the method which he employed is complicated and difficult. The technique described here appears to offer greater promise for practical application.

I should like to ask Dr. Denny whether nonspecific cross reactions can be absorbed out of the sera.

DR. FLOYD W. DENNY JR., Minneapolis: In general the complement-fixation method has not proved satisfactory for the demonstration of type-specific streptococcal antibodies, and we have not used it at all in our laboratory. The titers obtained with the hemagglutination technique are usually higher than those obtained with the precipitin method.

We have not tried to prevent nonspecific cross reactions by absorbing the sera with homologous erythrocytes.

Studies of Serum Electrolyte Changes During Exchange Transfusion in Infants with Erythroblastosis Fetalis. DR. GERALD MILLER, AUGUSTA B. MCCORD, PH.D., DR. HOWARD A. JOOS, and DR. SAMUEL W. CLAUSEN, Rochester, N. Y.

Potassium is known to pass from erythrocytes to plasma during storage of citrated whole blood. A study was therefore made of the effect of donor plasma on the serum potassium concentrations in eight erythroblastotic infants treated by exchange transfusion with stored blood.

In four cases the serum potassium concentration in the infant's blood was normal at the beginning of the procedure. The plasma concentration of potassium in the donor bottle was not greatly increased above normal (5 to 8 mEq. per liter), in keeping with the short storage period of one to four days. At no time during the procedure did the serum potassium concentration of any of these four infants exceed the normal values for our laboratory.

Four infants inadvertently received blood which had been stored for 9 to 21 days. In the donor bottles the plasma potassium concentration was 12 to 18.6 mEq. per liter. In two of these infants the serum potassium concentrations were normal at the beginning of the procedure. The respective donor bottles used for these two infants contained potassium concentrations (in the plasma) of 16 and 18 mEq. per liter. The high potassium concentration in the donor plasma resulted in progressive increase in the serum potassium concentration in these two infants. By the end of transfusion both infants' serum potassium concentrations had been raised to 8 mEq. per liter. In neither case was hyperkalemia diagnosed from the electrocardiogram at the time of the procedure, although in the tracing recorded for one infant there was a measurable rise in amplitude of the T waves from the beginning to the end of the transfusion, and in the other there was some cardiac irregularity and a brief period of asystole near the end of the procedure.

In one patient, an 1,100-gm. premature infant, prior to treatment the serum potassium was 8.2 mEq. per liter, the serum sodium 146 mEq. per liter and the calcium 6.0 mg. per 100 ml. The donor bottle had been stored 21 days, and the plasma contained a concentration of potassium of 18.6 mEq. per liter. The infant's serum potassium concentration did not fluctuate greatly during the course of the procedure, but electrocardiographic abnormalities were striking. At the beginning of the procedure there was definite electrocardiographic evidence of hypocalcemia, with a prolonged QT interval and lengthened ST segment. During the first 70 cc. exchange the hypocalcemic effect became more pronounced, and the amplitude of the T wave gradually increased until a 2:1 heart block appeared. The serum potassium concentration at this point was 9.1 mEq. per liter. The block was relieved and the T wave lowered by administration of calcium gluconate.

A fourth patient received blood in which the plasma potassium concentration was 12.3 mEq. per liter. Hyperkalemia did not develop in this baby, a fact suggesting that the smaller excess of potassium was rapidly removed from the blood stream.

In summary, exchange transfusion may at times induce simultaneous hypocalcemia and hyperkalemia. In view of the known physiological antagonism of these two ions under certain conditions, such a situation could be hazardous, particularly in patients in whom there exists either immaturity or impairment of renal homeostatic mechanisms. This potential risk can be minimized by the use of relatively fresh blood and the judicious administration of calcium during replacement transfusion with citrated blood.

DISCUSSION

DR. GEORGE M. GUEST, Cincinnati: The conclusion that Dr. Miller drew from his studies deserves emphasis: It is always wisest to use fresh blood for transfusion. The use of stored blood should be restricted to emergencies, as for quick replacement of blood lost by hemorrhage when the need is immediate and fresh blood is not available. Although methods for preservation of whole blood have been greatly improved in recent years, it must be remembered that progressive chemical changes in stored blood may make its use hazardous under certain conditions. The increased concentration of potassium in the plasma, to which Dr. Miller directed most attention, is only one sign of cellular deterioration. Under certain conditions increased inorganic phosphate also may be a toxic factor. In stored blood inorganic phosphate is liberated from labile organic phosphates of the cells and escapes into the plasma to an extent closely parallel with the increase of potassium.

Both clinical experience and experimental studies in animals have shown that with normal renal function a great deal of potassium phosphate can be administered intravenously with impunity and with benefit in some conditions (such as diabetic acidosis when body stores of potassium and phosphate have been depleted and when renal function remains normal); but when impaired renal function has led to hyperphosphatemia, hyperpotassemia and hyperazotemia, both experimental animals and human patients have been found to be extremely sensitive to intravenous injections of even small amounts of potassium and phosphate salts. Adrenalectomized animals also are sensitive to both.

It is difficult to generalize about the physiological state of erythroblastotic infants, even when clinical and hematologic signs are similar. Many undoubtedly have an essentially normal renal status. But, on the other hand, some show rapidly increasing concentrations of nonprotein nitrogen in the blood and increasing potassium and inorganic phosphorus in the plasma; hypocalcemia develops in some. Such infants are apt to be especially sensitive to toxic effects of blood that has a high plasma potassium and inorganic phosphorus.

Normal red blood cells have been shown to be capable of taking up potassium and inorganic phosphate from plasma (added in vitro or injected intravenously) with extraordinary rapidity. But in the presence of already existent hyperphosphatemia and hyperpotassemia, added potassium and phosphate are apt to aggravate the chemical imbalance. Thus the toxic effects of erythroblastotic infants receiving transfusions of blood with high plasma potassium and inorganic phosphate will undoubtedly vary considerably with the physiological states of the infants.

DR. LOUIS K. DIAMOND, Boston: Dr. Miller has pointed out one important concept in the exchange transfusion procedure, which, because of its common use in many clinics, has often been regarded rather lightly. Dr. Guest brought up the point that the sicker the infant the more likely he is to suffer from receiving relatively old blood and that, therefore, it is all the more important to use fresh blood in treating an infant who is quite anemic and may have kidney failure in addition to metabolic changes.

There are several other difficulties which we have learned, by experience during the past four years, to watch for in the use of exchange transfusion in treating erythroblastotic infants. There are, first, mechanical difficulties which, if the clinician or the operator is not acquainted with them, may defeat his ability to do successfully an exchange transfusion using the umbilical vein, the saphena or other vein. These are readily overcome by experience and practice.

One important consideration that Mollison of London pointed out several years ago and that we have learned to respect is the danger of the sudden death of an infant who is very sick when the transfusion is started if blood is pumped in too vigorously or too rapidly and he already has a high venous pressure. Withdrawal of 10, 20, or 30 cc. of blood, which is replaced with 30 to 50 cc. or more, may produce cardiac failure or sudden death of an infant with cardiac dilatation and other signs of circulatory collapse. It is, therefore, good practice not to remove more blood during administration of the first 100 cc. or more than one puts in, to follow the venous pressure carefully, and not to let it get too high at any point. In fact, it is better to leave the infant with a deficit at the end of the exchange of as much as 30 to 60 cc.

Dr. Miller mentioned the hypercalcemia, and, as in the case of the hyperpotassemia, it is important to follow this carefully. Common practice in our clinic is to give 2 or 3 cc. of calcium for every 100 cc. of blood rather than to wait until the end of the total exchange, at which time the calcium may be low and the sodium, from the large amount of citrated blood, may be relatively high.

I wonder whether Dr. Miller has followed the potassium in other infants, particularly those who were very anemic, to find out whether they have signs of potassium intoxication due to the rapid hemolysis of their own red cells that may take place either in utero just before delivery or in the first few hours after delivery.

DR. GERALD MILLER, Rochester, N. Y.: I should like to thank the discussants for their remarks.

In answer to Dr. Diamond's question about observations on the effect of erythrocyte potassium released during hemolysis in severely anemic infants, I can only say that we have no serial observations on such infants prior to therapy. It is interesting in this connection, however, that one of the infants in whom hyperkalemia occurred during exchange transfusion was a severely affected infant, quite anemic, with hemoglobinemia and methemalbuminemia, signifying intravascular hemolysis, despite which the serum potassium concentration was normal prior to therapy. Thus, until the time treatment was started the infant had been able to accommodate the potassium released during hemolysis of her own erythrocytes.

Erythroblastosis Fetalis: Serum Bilirubin. Dr. David Yi-Yung Hsia, Dr. Fred H. Allen Jr., Dr. Louis K. Diamond, and Dr. Sydney S. Gellis, Boston.

The experiences with serum bilirubin levels in 229 infants with erythroblastosis are presented. It was found that the majority of sensitized infants had cord bilirubin levels of 5 mg. per 100 ml. or even higher, though visible jaundice was never present at birth. Thereafter, the bilirubin level rose sharply and remained much higher than the levels seen with physiological jaundice in normal and premature infants. Clinically, the development of skin jaundice lagged behind the rise of serum bilirubin. Exchange transfusions markedly lowered the bilirubin levels.

Despite certain limitations, the data show a clear correlation between the development of kernicterus and the height of the serum bilirubin level. In the range of 0 to 5 mg. per 100 ml. there was no kernicterus. In the 6 to 15 mg. range there was an incidence of 3%, all cases being in infants whose only bilirubin determination was obtained in the first 2 hours of life and whose bilirubin certainly rose much higher in the next 24 hours. In the 16 to 30 mg. range, there was an incidence of 18%, and in the range of 31 mg. or higher, there was an incidence of 50% of kernicterus.

In the last 100 consecutive cases of erythroblastosis we attempted to keep the bilirubin level below 20 mg. in each case by doing multiple exchange transfusions if necessary. No cases of kernicterus were encountered in this series.

DISCUSSION

Dr. Irving Schulman, New York: Dr. Hsia's data necessitate a word of caution about a method of replacement transfusion which has appeared in the literature, namely, the use of packed red cells.

In evaluating this technique, we used it on seven infants before abandoning it. The cells had a hematocrit value of 60, and a one-volume exchange was used, based on an approximate blood value of 85 cc. per kilogram. Each of these infants showed a tremendous increase in icterus in two or three days after the replacement transfusion was done, and we therefore performed serial bilirubin determinations for five of them. At the peak of the icterus the bilirubin levels of all five were over 35 mg. per 100 ml.; one was 45 mg. and one 57 mg.

I think it is of interest that in two of these children the direct bilirubin constituted 30 to 40% of the total. One factor, of course, in a replacement transfusion with packed red cells is that one gets only 50 to 60% exchange, as opposed to the 85% obtained with the usual method.

In addition, with an indirect tagging method it appeared that a segment of the packed red cells was destroyed with extraordinary rapidity, and it would seem, therefore, that the use of the packed cells might tend to increase the tendency to kernicterus and hepatic injury. However, in none of these infants did kernicterus deevlop.

Dr. A. Ashley Weech, Cincinnati: I want to thank Dr. Hsia for presenting on a large scale carefully analyzed quantitative data. We also have been greatly interested in a possible relationship between the intensity of icterus in erythroblastosis and the involvement of cerebral nuclei. In looking back over the years I can remember no instance in which the serum bilirubin exceeded 80 mg. per 100 ml. and the infant escaped such involvement. However, I have observed one infant whose level rose to 60 mg. per 100 ml. and subsequent development was normal. I wonder whether Dr. Hsia can tell us what his experience has been in this regard.

We also believe that the intensity of bilirubinemia must be determined by analysis of serum. Does Dr. Hsia have an explanation for the frequent marked discrepancy between serum bilirubin concentration and intensity of jaundice?

We were at one time interested in the nature of the pigment that stains the basal ganglia. In one instance we obtained slices of stained brain and, using unstained portions of the same brain as a control background, made tracings of the color spectrum on a recording spectrophotometer. The pigment exhibited maximum absorption at 440 mμ, which is the same as that of bilirubin. The observation is suggestive, but of course not proof that the pigment is bilirubin.

DR. LOUIS K. DIAMOND, Boston: As Dr. Hsia has already mentioned, one reason why we are unable to answer many of the questions he himself proposed and others may ask is that we no longer have the material available to us in the sense that we try not to let hyperbilirubinemia develop or let the children run the risk of kernicterus.

We should have liked to run a control experiment such as Mollison suggested to us several years ago and such as he and his associates have been able to do in England and have recently reported in a preliminary paper. Most of our patients, however, are repeaters and come to us knowing that we will do everything we can for the children and knowing also that exchange transfusion is the method we usually use. We could not make controlled observations without controlled transfusions in such patients.

Dr. Hsia's suggestion, therefore, is valid. The only way we can collect data in this country is to have various observers in many clinics carry out bilirubin determinations by the new micromethod on capillary blood that Dr. Hsia has proved useful even with small infants. The results of such measurements should be pooled in an effort to determine at what day hyperbilirubinemia reaches its maximum level in children with uncomplicated erythroblastosis, at what level kernicterus may occur, and at what level it invariably occurs.

The use of packed red cells never seemed logical to us, because the chief reason for exchange transfusion is to remove the child's own coated or potentially destructible red cells, Rh-positive cells, as completely as possible. If that could be done without giving the baby blood, obviously, the procedure would be ideal, but one must replace in order to carry on normal red cell function. The second reason for exchange is to remove whatever free antibodies still exist, and we know an appreciable amount exist in the child's circulation and tissues. The third reason is to remove the blood pigment, which is not done if one merely uses packed red cells to a minimal degree and obtains an exchange of 60% or less.

In addition, as Dr. Schulman and Dr. Carl Smith have apparently found, the packed red cells, even the Rh-negative cells, may be destroyed more rapidly when blood is put in in this way than in incompatible transfusions. Completely compatible blood given to the patient who has agglutinable and agglutinated cells in his circulation is destroyed more rapidly because some of the infused cells are entrapped in the agglutinates that form and are destroyed during destruction of the incompatible cells. A similar destruction may occur in infants who are given packed cells, even though the blood seems compatible.

For this reason and for others, until such time as some other method is developed for treating erythroblastosis and for preventing the danger of kernicterus, exchange transfusion as complete as possible must be given in the first 24 hours to the patient who may have trouble and in the next 24 hours or even longer if hyperbilirubinemia occurs.

DR. RICHARD L. DAY, New York: The much smaller experience at Babies' Hospital confirms what has been said about the importance of bilirubin. We have been using a micromethod for bilirubin for a few months, and for some time have been taking a rapid rise of bilirubin as an indication for an exchange transfusion in the few babies who seem at birth to be too mildly ill to need one.

I was hoping someone from Johns Hopkins would comment on the role of direct or indirect bilirubin in kernicterus. My recollection is that cases of familial icterus and kernicterus without hemolysis were presented from that institution recently, and I believe the bilirubin in those cases was indirect.

DR. NEVA M. ABELSON, Philadelphia: Dr. Hsia and Dr. Diamond have called attention to the importance of pooling data from various clinics. I should like to add that over the past year we were so unfortunate as to see 13 cases of kernicterus in our clinic. In general, the maximum serum bilirubin levels were higher for children with kernicterus than for those without, but we observed three glaring exceptions to this generalization. In these cases the serum bilirubin levels of badly affected babies (and these were maximum observed bilirubin levels) were 8 mg. or under.

Therefore, we have been led to ask whether this is not an accidental rather than a cause-and-effect relationship.

In reply to Dr. Gellis, I am sorry to say that we used the serum bilirubin level as a criterion in deciding to exchange, or rather not to reexchange, the blood of an infant, and we did follow the serum bilirubin serially in that child.

DR. SYDNEY S. GELLIS, Boston: I should just like to reemphasize what Dr. Hsia has already pointed out, that bilirubin is at present merely being used as an indicator. There may not necessarily be any cause and effect between bilirubin and kernicterus, but until a better indicator is discovered, it would seem logical to use bilirubin levels as an index for replacement transfusion.

We should also like to know from Dr. Abelson when the levels of 8 mg. were obtained, because, as Dr. Hsia pointed out, the age at which the level is obtained is of prime importance. If this level occurs only in the first few hours of life, it may mean that the level is going to rise rapidly and is much more significant at that point than a higher level at 18 hours of life.

DR. DAVID Y. HSIA, Rochester, N. Y.: Regarding the high serum bilirubin level, we have not observed a baby with very high levels to whom we did not give exchange transfusions, so I am not able to say at what critical level kernicterus will definitely appear. On one occasion, I saw a baby with a serum bilirubin level of 30 mg. per 100 ml. at 6 hours of age, which is very high indeed, in whom kernicterus did not develop. He was treated by exchange transfusion.

As to Dr. Abelson's point, namely, whether the level of serum bilirubin can cause kernicterus under certain circumstances, I think the relationship is primarily one of time. We have in the last two weeks had occasion to take care of a baby to whom for other reasons we were not able to give exchange transfusions. We were able to follow the serum bilirubin level every six hours during the acute phase of the disease. The maximum level was 40 mg. per 100 ml. at the end of 60 hours. At 72 hours all the signs and symptoms of kernicterus developed. The serum bilirubin level six hours after kernicterus developed was only 15 mg. per 100 ml., indicating that apparently there can be falls in serum bilirubin levels in such infants. The levels therefore are significant only in terms of relationship.

I am pleased to hear from Dr. Weech about the pigment being thought to be bilirubin. We have ourselves tried to demonstrate that it is and so far have not been successful. We are hoping that with the use of the indirect bilirubin crystals, which have been perfected by the group from Johns Hopkins, we shall be able to do so one day.

I should like to say a word about the direct bilirubin question. We have found that when the one-minute bilirubin of Ducci and Watson is used all babies with erythroblastosis and those with physiological jaundice show only elevation of the indirect bilirubin. The direct, or the one-minute bilirubin, is never abnormal except in the inspissated-bile syndrome due to erythroblastosis, as pictured on the slide. This slide is from a case of inspissated bile. On the fourth day the one-minute bilirubin started to rise, and it reached 20 mg. per 100 ml. when the total bilirubin was 48 mg. per 100 ml., indicating obstructive jaundice. The jaundice cleared in four weeks.

We have recently done some work on bilirubin levels in premature infants without erythroblastosis. We found that some of these infants showed physiological jaundice with a bilirubin level of 24 mg. per 100 ml., which is above what we considered to be the critical level. We feel that perhaps some of the kernicterus reported in premature infants might be the result of this elevation, although we have no proof of that fact so far.

Effects of a New Vasodepressor ("Apresoline") on Blood Pressure and Renal Function in Children with Acute Nephritis. DR. W. W. MCCRORY, and DR. M. RAPOPORT, Philadelphia.

These observations concern the clinical evaluation of the hypotensive effects of oral and parenteral administration of a new antihypertensive drug, "apresoline" (Ciba), to six children with hypertension and acute nephritis and two patients with hypertension associated with chronic renal disease. The dose given by the parenteral route was 0.2 to 0.4 mg. per kilogram of body

weight. Oral administration in conjunction with parenteral injection was employed in five instances, the oral dose ranging from 50 to 200 mg. daily. In the majority of instances the parenteral administration of "apresoline" (hydrallazine hydrochloride) resulted in a fall in both systolic and diastolic blood pressure within 30 minutes. The fall in mean pressure ranged from 20 to 40 mm. Hg. The hypotension was regularly accompanied by tachycardia of some degree, and both effects persisted for two to four hours on the average. Side-effects included nausea and vomiting, orthostatic hypotension, dizziness, and some tachypnea. Subjectively there was relief of apprehension and headache. In one instance, severe vomiting and oliguria developed after two doses of "apresoline." This lasted for 36 hours with no further untoward effect. A prolonged hypotensive effect was observed. This is the first severe reaction noted to oral administration of this drug. Hematuria and urinary output have not otherwise been affected. Prolonged administration was associated with anorexia and nausea in one patient. Four of the six patients with hypertension accompanying acute nephritis had an excellent response on treatment with this drug. Results in the two patients with hypertension accompanying chronic renal disease were much less impressive. It is of interest that parenteral administration of "apresoline" was effective in temporarily inducing hypotension in one of these patients during a hypertensive encephalopathic crisis when parenteral administration of magnesium sulfate was without effect.

The changes in renal function and hemodynamics following parenteral injection of "apresoline" in doses of 0.15 to 0.4 mg. per kilogram were studied in seven patients in varying stages of acute nephritis and in one patient with hypertension and renal insufficiency. Using inulin clearance as a measure of glomerular filtration rate and *p*-aminohippurate clearance as a measure of effective renal plasma flow, we measured changes occurring in these two functions and in urine flow in response to parenteral injection of "apresoline" (dose, 0.15 mg. to 0.4 mg. per kilogram) in addition to changes in blood pressure and pulse. Parenteral injection of 0.15 mg. per kilogram did not produce a fall in blood pressure, and no change in inulin clearance from the control value was observed. A marked increase in effective renal plasma flow (*p*-aminohippurate clearance increased 46% over the control value) was observed in one of these subjects, and the filtration fraction decreased from 0.37 to 0.25. The patient did not have hematuria at this time, and neither patient was then hypertensive. Of the remaining five patients, three were hypertensive at the time of the observation and all but one had gross hematuria. The fall in mean blood pressure varied from 12 to 31 mm. Hg and was not related to dosage. A temporary decrease in glomerular filtration rate (inulin clearance decreased 19 to 72%) was observed in every instance and was maximal one hour after injection of the drug. Inulin clearance had returned to the control value in all but one instance by one and one-half to two hours after injection, even though some degree of hypotension persisted. Changes in renal plasma flow varied. A decrease in effective renal plasma flow (a decrease in *p*-aminohippurate clearance of 25 and 53%) was observed in two patients, no change in two, and an increase above control value (of 23%) in one. In all instances renal plasma flow returned to or exceeded the control rate by the close of the period of observation (one and one-half to two hours). A fall in filtration fraction occurred in all subjects, indicating some decrease in tone of the renal efferent arteriole. A decrease in urine flow was observed in every subject, being most marked in the subject with the greatest decrease in glomerular filtration rate. We cannot explain the mechanism of the temporary depression in glomerular filtration rate and urine flow observed in these patients following parenteral administration of "apresoline" in doses large enough to produce a fall in blood pressure. Even though "apresoline" administered parenterally decreases blood pressure and increases renal plasma flow, the total effect on renal function in these patients with acute nephritis was a varying temporary depression in renal excretory function. In one patient with hypertension and markedly reduced renal function due to chronic nephritis (inulin and *p*-aminohippurate clearance, 2.9 cc. a minute per 1.73 square meters) a fall in blood pressure produced by "apresoline" was not associated with a significant change in inulin or *p*-aminohippurate clearance or a decrease in urine flow. The absence of acute glomerulonephritis may be significant in this apparently favorable response.

DISCUSSION

DR. HENRY L. BARNETT, New York: In our experience, the use of magnesium sulfate in dosages suggested by Rubin and Rapoport has in most instances been quite effective. We, as others, however, have seen occasional children in whom adequate doses of magnesium sulfate are not followed by a fall in blood pressure, and I think there is a need for an additional drug in the treatment of this disease.

In the single instance in which we have used "apresoline," our observations tend to confirm those presented by Dr. McCrory. I think it is of great importance to know that, despite the fall in blood pressure, there may actually be an adverse effect on kidney function.

I should like to ask two questions. First, in the acute reaction to "apresoline," did any of the changes in function coincide with vomiting or other toxic effects which might themselves have influenced function apart from the drug? Second, I should like to ask Dr. McCrory whether he believes "apresoline" should be used in place of magnesium.

DR. S. A. KAPLAN, Cincinnati: Our group has had some experience with the use of "apresoline," although we have used it more frequently for toxemia of pregnancy than for acute nephritis. We have studied about 10 cases of toxemia and in all have encountered a significant lowering of the blood pressure without reduction of the renal plasma flow. Using the formulas of Gomez, we have calculated renal vascular resistances and, as Dr. McCrory has suggested, have found that "apresoline" produces dilatation of the afferent arteriole.

Our experience with acute nephritis is confined to one patient in whom hypertension persisted for nearly four weeks despite the use of adequate doses of magnesium sulfate. After administration of an initial dose of "apresoline" intravenously the diastolic pressure fell at once but the systolic pressure remained unchanged. We continued to administer "apresoline" orally for three weeks, at the end of which time his systolic pressure, too, had returned to normal. We made no measurements of renal hemodynamics in this case.

DR. JACK METCOFF, Boston: Drs. McCrory and Rapoport are to be congratulated on an excellent study of a common disease about which we have little information. I have a few questions.

First, I wonder whether Dr. McCrory had an opportunity to make similar measurements during the administration of magnesium sulfate, particularly during its intravenous administration. Second, I wonder whether azotemia occurred in patients who received repeated doses of "apresoline." Third, with repeated doses effecting reductions in renal function, was either escape or persistent decremental fall in renal function observed with each administration? Fourth, did the diuresis which tends to occur after seven or eight days of acute glomerular nephritis still occur despite fall in renal function and in association with constriction of the arterioles?

Finally, I wonder whether the calculations of resistance have much significance, particularly if they are based upon Gomez' formula or involve others, like Lamport's, which depend upon the integrity of the glomerular membrane. Obviously, the membrane is distorted in this disease.

Has anyone had an opportunity to measure cardiac output during these times?

DR. HORACE L. HODES, New York: Dr. Riley is not here to speak, so I should like to report one observation which he made. He found that a child who had Riley-Day disease with hypertension received "apresoline" without any effect. I wonder whether Dr. McCrory would like to speculate about this observation.

DR. W. W. MCCRORY, Philadelphia: This slide was made before we totaled all our figures. (A slide was shown.) As can be seen, the child went through a course of hypertension in acute nephritis. This slide is purposely shown to draw no conclusions. The changes in blood pressure, if all the peaks were taken out, would mimic rather nicely the changes in weight, so that as the child's disease became worse and improved, so did his blood pressure, in spite of repeated doses of "apresoline," each of which produced a nice clinical response. He was quiet and happy. He went through a perfectly normal course with no decrease in urinary output

on repeated parenteral administration. We have given this drug for as long as three weeks to patients with acute nephritis without development of observable increases in nonprotein nitrogen.

I think one decides in terms of the drug's use as to which is worse—the temporary depression in renal function or the dangers of uncontrolled hypertension.

In answer to Dr. Barnett's question, I purposely showed the severest response. The child reacted violently to our whole procedure, and I am sure that much of his reaction was psychic. That was not true of other subjects.

I have seen the data of Page and his group in Cleveland, and among 26 patients who received "apresoline" intravenously, renal function studies of about 12 showed decreases in glomerular filtration rate of from 10 to 25%. These were not of the range we have seen in acute nephritis, but evidently such decreases can occur, and they were usually associated with an increase in renal blood flow.

In answer to Dr. Metcoff, we did not calculate any resistance. I should have put quotes around the figures "efferent resistance increase and decrease."

We did measure by ballistocardiograph the cardiac output in one of our subjects. Our calculations would lead us to believe that it increased about 25%, so this would not explain the fall in clearance.

Differentiation of Infection by Coxsackie and Herpes Simplex Viruses. Dr. Edward C. Curnen and Dr. Mary O. Godenne, New Haven, Conn.

The Coxsackie viruses are a group of filtrable agents which cause human disease. They have in common certain properties, including a particular pathogenicity for newborn mice and hamsters, in which they characteristically induce myopathy. These viruses are widely distributed and represent at least 15 distinct entities or "types" which differ antigenically and in other respects.

In an investigation continued over a period of two years, pharyngeal swabbings, feces, and other specimens collected from 880 patients were tested in newborn mice for the presence of viruses. Strains of virus were recovered from 54 patients. Among these strains, 44 were ultimately identified as Coxsackie viruses, 1 as vaccinia virus, and 9 as herpes simplex virus. The ease with which the last-named agent was isolated from suckling mice and the similarities of infection induced by it and certain Coxsackie viruses in these animals and in man prompted a comparative study of herpes and Coxsackie viruses.

In this series, isolations of herpes virus were distributed throughout the year, whereas 89% of the Coxsackie strains were encountered from July through November. Strains of Coxsackie virus were recovered from 9 patients with herpangina who had vesicles or ulcers on the fauces, tonsils, or palate and from the pharynx of 21 patients without distinctive lesions. Herpes virus was isolated from seven patients with oropharyngeal lesions. In one the clinical findings were typical of herpangina; in six the lesions were distributed differently or were also present on the skin. Herpes virus was recovered from cutaneous vesicles of two patients.

In the laboratory, both prototypes and recently isolated strains of Coxsackie and herpes viruses were compared for viral activity under a variety of circumstances. Each strain was identified in neutralization tests with specific immune sera. The strains of Coxsackie virus represented 15 different immunologic types. After exposure to ether for 18 hours at 4 C., all 41 strains of Coxsackie virus remained active, whereas 12 strains of herpes virus became inactive. Lesions of striated muscle similar to those induced in suckling mice by Coxsackie viruses were not observed in mice infected by herpes virus. The results of tests in adult mice for the capacity to cause fatal infection by the intracerebral route within 12 days were negative with 40 strains of Coxsackie virus and positive with each of 10 strains of herpes virus. Following inoculation on the cornea of rabbits, keratoconjunctivitis was induced by 10 strains of herpes virus and not by 17 strains of Coxsackie virus. All strains of herpes virus which propagated in suckling mice mutiplied when inoculated on the chorioallantoic membrane of chick embryos. In tests with 17 strains of Coxsackie virus, viral activity of the membranes was demonstrable in suckling

mice with 10 strains after one egg passage, with 5 strains after an additional passage, and with 2 strains after three passages.

These findings provide additional information concerning the biologic characteristics of Coxsackie and herpes simplex viruses and criteria for differentiation of infection by these agents.

DISCUSSION

DR. ALFRED L. FLORMAN, New York: This report by Dr. Curnen points up the need to go further than to assume that a specimen which produces a disease in suckling mice must contain one of the Coxsackie viruses. I think he has done a very pretty job in going through a great mass of material.

The use of ether as a means of differentiating between various viruses has been known. Several years ago, together with Dr. Enders we were able to show that vaccinia virus, which was one of the viruses considered by the authors, is resistant to ether and that treatment with this chemical permitted separation from contaminating bacteria.

The talk that Dr. Hodes gave yesterday also emphasized the fact that agents other than the Coxsackie viruses may produce disease in suckling mice.

DR. ALBERT B. SABIN, Cincinnati: Dr. Curnen has shown very nicely how to differentiate in the laboratory between the herpes simplex and Coxsackie viruses. Many of you may wonder, as I am wondering, what the clinical implications of these findings are.

I was struck by the remark that a herpes simplex virus was recovered from a patient presenting the clinical manifestations of herpangina, namely, vesicles limited to the palate and pharyngeal wall. Is it possible that sometimes one may not be able on clinical grounds alone to differentiate between a primary herpetic infection and a Coxsackie-herpangina type of infection? I would appreciate it very much if Dr. Curnen would indicate whether in this case the disease was caused by the Coxsackie virus or the herpes virus.

The recovery of herpes simplex virus from the throat is not in itself evidence that this virus is responsible for the pathological condition. I will never forget that when we tried to adapt measles virus to mice we obtained a virus from the oral washings. What was it? It was herpes simplex virus which the patient with measles was apparently carrying. That is nothing new.

The question is, in the patient with the herpangina syndrome from whom herpes simplex virus was recovered, which virus caused the herpangina syndrome? Herpes simplex or Coxsackie?

DR. A. J. RHODES, Toronto, Canada: I should like to ask Dr. Curnen one or two specific questions. I was rather surprised by his results with ether and wonder whether ether and glycerin behave in the same way. I had always believed that herpes was one of the viruses which withstood ether, and I have been telling students for years that if they were going to send brains from possible cases of nervous infections, they could quite safely send them in glycerin, thinking that herpes, as well as other viruses, would maintain activity by that technique. Is it possible that these dermal strains of herpes simplex are apparently killed by ether whereas certain other strains are not?

Another question is about adult mice dying from Coxsackie infection. I have been under the impression that sometimes adult mice do die, particularly when immunized against Coxsackie viruses to produce serum.

Another question is, have you ever recovered herpes virus from stools? Such recovery would be a serious difficulty in some of this work. Stools are used perhaps more widely than pharyngeal washings.

DR. EDWARD C. CURNEN, New Haven, Conn.: In reply to Dr. Florman's comment, we did find that the one strain of vaccinia virus encountered in this series was resistant to treatment with ether.

In answer to Dr. Sabin, we recovered herpes virus and not Coxsackie virus from only one patient with herpangina. With sera from the patient, an increase in antibody against herpes virus was demonstrated. We did not test sera from the patient for antibodies against all of the

different Coxsackie viruses. I agree that the findings do not exclude the possibility that this patient may have been infected with a Coxsackie virus in addition to herpes virus.

In reply to Dr. Rhodes, all the strains of herpes virus which we studied, including some of the standard strains, were tested for resistance to treatment with ether. By the methods outlined, none of these herpes strains were found to be resistant. I agree with Dr. Rhodes that sometimes adult mice do die after infection with Coxsackie virus. In the present study deaths did not occur among mature mice during the 12-day period of observation following a single injection. On the other hand, deaths were observed in adult mice given repeated injections for the purpose of immunization, usually, however, after more than one injection and later than the 12th day following the initial injection.

We did not isolate herpes virus from the specimens of feces, but I believe others have recovered this agent from stools. Irrespective of the source of virus, however, it should be possible to differentiate a strain of herpes virus from a virus of the Coxsackie group by the procedures outlined.

Production of Congenital Abnormalities in Mice by Alloxan. Dr. Oscar A. Ross and Dr. Samuel Spector, Cleveland.

The cause of the abnormalities which are found in the infant born of a diabetic mother is not known. The fact that these abnormalities also occur in the infant born of a prediabetic mother suggests that they result from factors other than those commonly associated with the diabetic state. In recognizing some parallelism between alloxan diabetes in the animal and diabetes in the human, we found it interesting to see what effect small subdiabetogenic doses of alloxan might have in the pregnant mouse.

At the end of an isolation period, virgin white female mice, aged 6 to 8 weeks and weighing approximately 20 gm., were mated over a three to four day period. Injections of 100 to 150 mg. per kilogram of body weight of alloxan buffered at pH 7.2 were given to the mice subcutaneously on three successive days. At an estimated gestation period of 18 days (± 2) the mice were sectioned, and the fetuses were immediately fixed in formalin. Of 24 mice so treated, 1 had a normal litter, 6 had litters of uniformly small but normal-appearing fetuses, 2 had litters of uniformly large fetuses, and 15 had litters which contained at least one abnormal fetus. The 24 pregnancies resulted in 206 fetuses, of which 61, or 29%, showed some gross abnormality. The most frequent defect was failure of development in part or in whole and resulted in poorly differentiated fetuses, many of which were macerated. In five litters there were fetuses with a head defect which suggested a myeloencephalocele. In four litters macrosomia was evident.

DISCUSSION

Dr. George M. Guest, Cincinnati: I believe that Dr. Spector did not clearly differentiate diabetogenic effects and histotoxic effects of alloxan when discussing the influence of alloxan diabetes on fetal development. It seems to me likely that the histotoxic effects of the alloxan may have been more important than the hyperglycemia of the diabetic state in producing the developmental defects described.

I regret that Dr. Warkany is not present to discuss this paper, but I should like to emphasize a point that he considers important in such studies, namely, that it is necessary to define the period of gestation as closely as possible. Warkany has shown that the critical period in gestation when fetal developmental defects are established or can be prevented may be extraordinarily short. He found, for example, that in riboflavin-deficient rats there was a critical period around the 15th day, before which time the administration of riboflavin could prevent fetal abnormalities; but after the 16th day the administration of riboflavin did not prevent the abnormalities. In order to know more exactly the critical time at which injections of alloxan in the pregnant mice produced fetal abnormalities it would be desirable to establish the date of conception as definitely as possible. Likewise, in order to define more exactly the critical period at which fetal damage is produced, it might be advantageous to induce diabetes by a single injection of alloxan (intravenously, after a period of fasting) as is commonly done in rats, rather than by repeated subcutaneous injections given over a period of four days.

DR. ALTON GOLDBLOOM, Montreal, Canada: We have reached a stage, it seems to me, where we are now differentiating between the factors of heredity and the factors of toxicity in the causation of congenital defects, and I have been inclined to agree with Dr. Guest's statement that we must be careful in differentiating the histotoxic effects from others.

Many histotoxic substances have been demonstrated to be responsible for the production of congenital anomalies. In our clinic, Frazer and Fainstat found that they could produce virtually at will a cleft palate in a strain of mice known not to be susceptible to this anomaly by administration of cortisone, provided it was given before the 16th day of gestation. That is one other instance, probably, of a histotoxic substance which is responsible for the production of congenital anomalies.

In the literature that Dr. Spector reported relative to increased size, I wonder whether the dose of alloxan was sufficient to have a diabetogenic effect and whether the increased size was not due to that factor.

DR. SAMUEL SPECTOR, Cleveland: I want to thank Dr. Guest and Dr. Goldbloom for their comments. In regard to the first point raised by Dr. Guest, I think we tried to make it clear, at least in the introduction, that we were not interested in producing overt diabetes, for we know that in the human anomalies are apt to occur as frequently in infants born of the prediabetic as in those born of the diabetic woman. By the use of small doses of alloxan we were trying to simulate the prediabetic state. It became a matter of speculation whether there is an alloxan-like substance in the prediabetic woman which, though it may require years to produce diabetes mellitus, may nevertheless affect the embryo and fetus in development. We were well aware that alloxan would probably have a histotoxic effect on the embryo, but we wanted to demonstrate that this effect would occur at a dosage too small to produce diabetes in the mouse.

In regard to the critical point, this was the first trial run and we were more interested in whether the alloxan would produce anomalies than in obtaining an evaluation as to the exact time during gestation when these changes might occur. I think it is important to repeat the procedure, determining the critical point, and also eliminating, by perhaps increased dosage of the various B complexes, the possibility that a deficiency in vitamin B plays any role in the production of the anomalies. My own feeling is that alloxan produces the anomalies through a direct histotoxic effect on the embryo. Whether there is a similar substance active in the prediabetic or the diabetic human is unknown.

In answer to Dr. Goldbloom's question, the mouse that produced the litter showing macrosomia received the same dose of alloxan as others and before section showed a blood sugar level of 137 mg. per 100 ml. It was not a fasting blood sugar determination and so would have to be considered within normal limits. Therefore there was no evidence that that particular mouse had hyperglycemia. We did examine the pancreases of five of our treated mice, and none of them showed changes in the beta cells.

(To Be Concluded)

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

SUSCEPTIBILITY OF BACILLUS HEMOPHILIS PARAPERTUSSIS TO CERTAIN ANTIBIOTICS. E. DAY, and W. L. BRADFORD, Pediatrics **9**:320 (March) 1952.

The in vitro and in vivo susceptibility of Bacillus parapertussis to a number of antibiotics was studied. The in vitro tests were performed by growing standard amounts of a suspension of the organism on Bordet's medium to which various concentrations of the antibiotic had previously been added. After an incubation of 72 hours the degree of growth inhibition was observed. The in vivo tests were carried out by testing the protective value of daily injections of various amounts of the antibiotic against a standard infecting dose of the organisms given intranasally to mice. The authors summarize their study as follows:

The susceptibility of 12 strains of H. parapertussis to certain antibiotics was examined.

In vitro, the antibiotics in order of their decreasing activity were polymyxin B, terramycin, chloramphenicol, aureomycin, neomycin, penicillin, and streptomycin. There was little variation in the response to any one antibiotic of the various strains tested.

In vivo, the antibiotics listed in the order of their decreasing effectiveness against the experimental murine infection were polymyxin B, aureomycin, terramycin, neomycin, chloramphenicol, and streptomycin.

B. parapertussis was more resistant than Hemophilus pertussis to each antibiotic tested in vitro. In vivo, similar degrees of effectiveness were exhibited against the two organisms by polymyxin B, terramycin, and chloramphenicol; the first two antibiotics named being particularly effective both in vitro and in vivo.

FROM THE AUTHORS' SUMMARY.

AN ANTIBIOTIC (ANTIMYCOTIC) METABOLIC PRODUCT OF ESCHERICHIA COLI. O. THALHAMMER, Helvet. paediat acta **6**:523 (Dec.) 1951.

If the growth of coliform bacteria in the stool is arrested by oral administration of streptomycin, fungi of a saccharomycetic (yeast-like) type appear in excess in the stool flora; if the coliform flora returns, the fungi disappear. On the basis of this observation and of general biological considerations, strains of Escherichia coli were studied for the presence of metabolic products antagonistic to the formation of fungi. It was shown that numerous strains cultivated fresh from the infant's stool are able to retard the growth of fungi. This characteristic, however, disappears after several culture passages. The Esch. coli strains which retard the growth of fungi are recognizable by the discoloration which they cause on bromothymol blue-sucrose agar. A similar discoloration by chemical means, i. e., merely a change in the pH of the culture, does not inhibit the growth of the fungi. It is surmised, therefore, that a basic antimycotic substance of an antibiotic character appears in the metabolism of certain Esch. coli strains.

FROM THE AUTHOR'S SUMMARY.

LYSOZYME IN THE BLOOD SERUM, SPINAL FLUID, AND PLEURITIC FLUID IN SOME DISEASES OF CHILDHOOD. G. MAINI, Lattante **23**:13 (Jan.) 1952.

In this study the bacteriolytic capacity of blood serum, spinal fluid, and pleuritic fluid toward the Micrococcus lysodeikticus was determined and recorded in Fleming units. The lysozyme content of the blood of patients with pneumonia, empyema, and purulent meningitis was very high. In the same patient, the titer was approximately the same in the blood and in the pleuritic fluid in empyema, and in the blood and in the spinal fluid in purulent meningitis. The titer was low in the various types of tuberculosis and in typhoid.

HIGGINS, Boston.

IN VITRO TESTS OF THE SENSITIVITY OF SOME TYPES OF ENTEROBACILLI TO ANTIBIOTIC THERAPY AND CHEMOTHERAPY. G. R. BURGIO and A. ALBEGGIAMI, Pediatria **60**:1 (Jan.) 1952.

Comparative in vitro tests were made of the action of certain antibiotics (streptomycin, chloramphenicol, aureomycin, terramycin, and penicillin) and that of chemotherapeutic agents (sulfaguanidine, sulfomethylthiazole, parasalicylic acid) on 41 strains of enterobacilli from infants with acute enteritis and 32 strains from patients with appendicitis. Streptomycin was effective against the Shigella organisms but relatively ineffective against Proteus or colon organisms. Penicillin was relatively ineffective against any of the enterobacilli. Charts are given showing the concentration of each antibiotic or chemotherapeutic agent necessary for bactericidal or bacteriostatic action.

HIGGINS, Boston.

MUS MUSCULUS LINNAEUS, PRIMARY RESERVOIR OF LEPTOSPIRA. A. CURBELO, F. SOTOLONGO, and V. MÁRQUEZ, Rev. cubana pediat. **11**:290 (May) 1949.

The authors report the finding of a considerable incidence of Leptospira infection among the common house mice in Cuba, their interest proceeding from the discovery of such infection in the home of a patient with a proved case of the disease.

They believe it important that this source be reported, as the rat is usually considered the primary reservoir of Leptospira icterohaemorrhagic and the common house mouse is little considered.

NELSON, San Francisco.

STUDIES ON BACTERIUM BIFIDUM [LACTOBACILLUS PARABIFIDUS] IN HEALTHY INFANTS: A CLINICAL BACTERIOLOGICAL INVESTIGATION. E. FRISELL, Acta paediat. (Supp. 80) **40**:21 (April) 1951.

Lactobacillus parabifidus (Bacterium bifidum) occurs both in breast-fed infants and in infants not fed on breast milk.

The L. parabifidus count is higher in breast-fed infants than in infants not fed on breast milk, the difference being statistically significant.

The L. parabifidus-stimulating property of breast milk will be lost if such milk is heated to a temperature of 100 C. or pasteurized at a temperature of 68 C. for 10 minutes. The difference with respect to breast-fed infants and infants fed on heated breast milk during the first month of life is statistically significant.

If an infant is fed on heated breast milk, L. parabifidus will adapt itself to conditions in the bowel, and after one or two months will increase progressively to the level occurring in breast-fed infants. The rise in the L. parabifidus count proceeds both in full-term and in premature infants, though not with the same regularity in the latter.

Examination of infants at different ages and at different stages of weaning seems to show that a L. parabifidus count corresponding in principle to that found in breast-fed infants may occur as long as the amount of breast milk suckled daily exceeds approximately 200 gm.

The number of "other bacteria" is lower in breast-fed than in bottle-fed infants of the same age. The difference, calculated on the number of bacteria growing on dextrose agar, is statistically significant.

The number of "other bacteria" is lower in breast-fed infants than in infants of the same age fed on heated breast milk. The difference, calculated on the number of bacteria growing on dextrose agar, is statistically significant.

A close correlation exists between the pH and the odor of the feces. Feces with pH values lower than 6 are attended by an acid odor, and feces with a pH values higher than 7, by a fecal odor; pH 6 and 7 are borderline values between which the conditions vary.

L. parabifidus appears to be of little significance in relation to the pH of the feces. This is indicated, for instance, by the fact that heated breast milk initially gives the same pH as milk suckled direct from the breast, but only 10% of the number of L. parabifidus organisms associated therewith.

No correlation seems to exist between the L. parabifidus count and the number of "other bacteria," either in breast-fed or in bottle-fed infants.

Both α- and β-lactose, when administered by mouth to children between the ages of one month and 2 years, seem capable of producing in certain cases a moderate increase in the L. parabifidus count. The increase is not significant. No difference has been found in this respect between α- and β-lactose.

The L. parabifidus count and the number of "other bacteria" are lower in children over one year old fed on mixed diets than in bottle-fed infants. The difference in each case is statistically significant.

L. parabifidus is strongly inhibited in vivo by aureomycin and chloramphenicol. With a dose of approximately 40 mg. per kilogram of body weight a day, the L. parabifidus count decreases by 90% or more.

L. parabifidus is inhibited in vivo by penicillin. With the same daily dose, the effect appears to be stronger with oral than with parenteral (intramuscular) administration.

L. parabifidus is completely inhibited in vitro by a sulfonamide ("elkosin") in a concentration of 3.3, but not of 1.32, mg. per milliliter; by penicillin in a concentration of 1, but not of 0.25, unit per milliliter, and by streptomycin in a concentration of 50, but not 10, mg. per milliliter.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

VITAMIN A POISONING. D. GRIBETZ, S. H. SILVERMAN, and A. E. SOBEL, Pediatrics **7**:372 (March) 1951.

Two cases of hypervitaminosis A are presented, together with a review of the experimental and clinical literature.

In the first case the highest reported fasting plasma vitamin A level was presented, the increase being chiefly due to a high vitamin A alcohol fraction. This elevated level of alcoholic vitamin A probably denotes large stores of vitamin A in the liver, and data are given to show that it is a better index of hypervitaminosis A than is the total vitamin A level. In addition, evidence is presented that the toxic factor in hypervitaminosis A is the permanent raised plasma vitamin A level.

The similarity between the experimental results in animals and the observations in the authors' first case is shown.

The important points necessary for making a diagnosis of hypervitaminosis A are discussed, and several similar conditions are differentiated.

It cannot be emphasized too strongly that excess vitamin intake may be as dangerous as a deficient intake.

FROM THE AUTHORS' SUMMARY.

Prematurity and Congenital Deformities

CARDIOVASCULAR DISEASE IN MARFAN'S SYNDROME [ARACHNODACTYLY], R. J. MARVEL and P. D. GENOVESE, Am. Heart J. **42**:814 (Dec.) 1951.

The authors report on the necropsy in a case of arachnodactyly and summarize the cardiovascular findings in 28 necropsies gathered from the literature.

Definite cardiovascular lesions were found in 25 cases. Left-ventricle hypertrophy was present in 19 cases, in 17 of which it appeared that valvular deformity was responsible for the hypertrophy. The microscopic changes ranged from hypertrophy alone to hypertrophy with varying degrees of fibrosis, necrosis, and cellular infiltration.

Congenital cardiac malformations were found in 16 of the 28 cases in which necropsy was done. Aortic aneurysms were described in 16 instances. The varied and numerous findings may be a manifestation of the many developmental disturbances of arachnodactyly.

GIBSON, Chicago.

CHEMICAL DEVELOPMENT IN UTERO. E. M. WIDDOWSON, and C. M. SPRAY, Arch. Dis. Childhood **26**:205 (June) 1951.

The tissues of 13 immature fetuses and 6 stillborn infants weighing more than 3,000 gm. were analyzed for nitrogen, fat, sodium, potassium, calcium, magnesium, phosphorus, iron, copper, and zinc, and the iodine in the thyroid gland was determined. The placentas of 12 of the fetuses and infants were also studied.

The fetus begins to lay down fat when it weighs 800 to 1,000 gm., and by the time it weighs 3,000 gm. the amount of fat in its body is approximately equal to the amount of protein (12%). After this the fat increases much more rapidly than the protein, and the body tissues of one stillborn infant which weighed 4,375 gm. contained 28% of fat.

The concentration of sodium per 100 gm. of fat-free body tissue decreased until the fetal weight was about 2,000 gm., and then it remained constant until term. The value reached was the same as that in adult life. The concentration of potassium in the fat-free body tissue increased throughout intrauterine life, but the concentration in the whole body altered little from the time the fetus began to lay down fat.

The concentration of calcium and phosphorus increased with increasing weight, so that the percentage of calcium at full term was rather more than twice, and that of phosphorus a little less than twice, as high as it was in the fetuses weighing 200 to 300 gm.

The percentage of iron and copper in the fetus increased with development, while that of zinc did not change. The liver and spleen contained about one-half the copper, one-fourth the zinc, and one-eighth the iron in the whole body.

The concentration of iodine in the thyroid appeared to increase during fetal life and after, and in the thyroid of three adults it was about 20 times as high in those of the immature fetuses.

At the 17th to the 19th week of pregnancy the fetus and its placenta were of approximately equal weight, and they contained similar amounts of nitrogen, fat, and potassium. During the last four months the fetus grew much more rapidly, so that at full term it weighed five or six times as much as its placenta. The "concentrations" of nitrogen and potassium were similar in the fetus and the placenta, but those of fat, calcium, magnesium, phosphorus, copper, and zinc were all higher in the fetus than in its placenta.

KELLY, Milwaukee.

CASE OF GARGOYLISM. H. JELKE, Ann. pædiat. **177**:355 (Dec.) 1951.

The author describes a classic case of gargoylism in a 6-year-old boy with disproportional dwarfism, gruesome facies, lumbar kyphosis, heart disease, enlargement of the liver and spleen, large umbilical hernia, elongated sella turcica, and imbecility. The child also had had cheilognathopalatoschisis.

The histopathologic picture, as described in the recent literature, lends support to the concept of gargoylism as a storage disease, but in no way to the old view of the stored substance as being simply a lipid. Except in the nervous system it seems, on the contrary, to consist of a complex carbohydrate (polysaccharide). In this respect it is of interest to note that the glucose tolerance test made in the case under discussion gave a blood sugar curve of a shape (flat and delayed) often seen in glycogen disease (glycogenosis; von Gierke's disease).

FROM THE AUTHOR'S SUMMARY.

ABORTIVE FORM OF MUTATION DYSOSTOSIS (DYSOSTOSIS CLEIDOCRANIALIS). E. HAUSMANN and R. SEYSS, Helvet. paediat. acta **7**:193 (April) 1952.

On the basis of one case, the author describes the symptomatology of cleidocranial dysostosis. Emphasis is placed upon the fact that the disturbance affects not only membranous but also, to a less extent, endochondrodiaphysial ossification. Investigation of the parents and siblings disclosed no further full-blown cases of the disease but did reveal in the mother and all the siblings variations from the normal which could fit into the general outlines of cleidocranial dysostosis. The malformation of the ear in the child first investigated could be traced back to the father. Particular reference is made to the hereditary aspects of the disease, and the possibility of the combined occurrence of this and multiple other degenerative stigmata is discussed.

FROM THE AUTHORS' SUMMARY.

HURLER'S SYNDROME: TWO CASES IN SIBLINGS. F. HURTADO, L. EXPÓSITO, and A. DE FERIA, Rev. cubana pediat. **11**:633 (Nov.) 1949.

The cases of two siblings, a girl aged 8 and a boy aged 5 years, with the classic findings of lipochondrodystrophy are reported. Complete case summaries, photographs, and good x-ray reproductions are included. These are the third and fourth cases of Hurler's syndrome to be reported in Cuba.

NELSON, San Francisco.

Newborn

MANAGEMENT OF ERYTHROBLASTOSIS FETALIS. C. E. SNELLING, and others, Canad. M. A. J. **66**:356 (April) 1952.

Various methods of management of the erythroblastotic infant are discussed. The authors obtained approximately the same results with repeated small transfusions and with replacement. They favor the replacement method but use it only if the baby is seen in the first 12 hours of life.

The authors are not of the opinion that the antibodies present in breast milk have any effect on the baby. They point out that premature delivery, to spare the baby, results only in a premature baby and has no effect on the erythroblastosis.

McGUIGAN, Evanston, Ill.

Acute Contagious Diseases

COMBINED IMMUNIZATION OF TUBERCULOUS CHILDREN AGAINST DIPHTHERIA, PERTUSSIS, AND TETANUS. M. WEICHSEL and A. HODES, J. Pediat. **37**:201 (Aug.) 1950.

Tuberculous children can be immunized against pertussis, diphtheria, and tetanus without danger of exacerbation of their tuberculosis. Satisfactory serum levels of diphtheria and tetanus toxoids were obtained in children given a combined antigen. The best results were obtained with the use of a material containing 20 Lf (limit-of-flocculation unit) of purogenated diphtheria toxoid, 12 Lf of purogenated tetanus toxoid, and 10,000,000,000 alum-precipitated pertussis organisms per dose ("tri-immunol"). Injections were given at three- to four-week intervals.

MacDONALD, Pittsburgh.

SUSCEPTIBILITY TO PENICILLIN AND TO SULFONAMIDES OF EIGHTY-TWO CULTURES OF HEMOLYTIC STREPTOCOCCI ISOLATED FROM THE FAUCES OF SCARLET FEVER PATIENTS. A. POUCHÉ and B. CARLETTI, Minerva pediat. **3**:535 (Oct.) 1951.

All 82 cultures of hemolytic streptococci from scarlet fever patients failed to grow in media containing 0.01 unit of penicillin per cubic centimeter but did grow in cultures containing 25 mg. per 100 cc. of sulfonamides (a mixture of sulfamerazine, sulfathiazole, and sulfapyridine). These in vitro experiments confirm clinical findings that the sulfonamide drugs are not so efficacious as penicillin in treatment of patients with scarlet fever.

HIGGINS, Boston.

TRIAL OF VACCINE-SERUM THERAPY IN TREATMENT OF POLIOMYELITIS. M. BENVENUTI, Riv. clin. pediat. **47**:137 (Feb.) 1949.

The author reports the encouraging results obtained in treatment of poliomyelitis with use of the serum of the mother's blood and rabies vaccine. Since only five patients were tested, one can make only very prudent assertions. The author calls the attention of his colleagues, especially pediatricians, to this treatment, which does not seem to be without some hope of success.

FROM THE AUTHOR'S SUMMARY.

MEASLES PROPHYLAXIS WITH GAMMA-GLOBULIN. R. ROSSI, Riv. clin. pediat. **48**:305 (March) 1950.

The reports in previous literature on the prophylactic action of the gamma-globulins in measles have been confirmed by the author. He is therefore in favor of their use, but would restrict it to specific cases.

FROM THE AUTHOR'S SUMMARY.

RUBELLA AND DEAF-MUTISM IN SWEDEN. BERTEL IVSTAM, Acta oto-laryng. **39**:380 (Oct.) 1951.

An analysis was made of 538 pupils attending a school for deaf-mutes in Sweden. There were in the series 261 children with deaf-mutism of doubtful origin. Twelve per cent of the mothers of this group had rubella within the first four months of pregnancy. In the years (1937 and 1941) when rubella was common the mothers of more than 10% of children had rubella. In Sweden the apparent incidence of deaf-mutism from rubella runs about 3 to 5%; that of the total malformations from this cause, 10 to 20%.

The frequency of these difficulties justifies deliberate infection of young girls with rubella and the use of convalescent serum or gamma-globulin to pregnant women exposed to rubella.

LEWY, Chicago [A. M. A. Arch. Otolaryng.].

Acute Infectious Diseases

CORTISONE AND CORTICOTROPIN (ACTH) IN TREATMENT OF RHEUMATIC FEVER. A. L. JOHNSON, M. F. MCCALL, E. R. HARPER, and others, Canad. M. A. J. **66**:225 (March) 1952.

The results of treatment of 39 children with rheumatic fever are reported. Follow-up periods ranged from 3 to 16 months. Treatment consisted of intramuscular or oral administration of cortisone or corticotropin. In 50 patients symptoms recurred four to six days after cessation of treatment. Four others had recurrences one to six months later. Five children showed no response. Nine were treated in recurrent acute attacks; their response was no different than that of children who had not had previous attacks. Prompt response was noted in 34 of the cases as regarded fever, pulse rate, arthritis, and sedimentation rate. Five children with chorea showed improvement during therapy, but in only one of these was it definitely established that the treatment was responsible.

The condition of seven patients with acute carditis was much improved within 48 hours. Two of them left the hospital without evidence of cardiac involvement. The heart size decreased in four patients. Of 17 patients with significant murmurs, a change was noted in 7.

Almost all the patients showed side-effects of treatment.

MCGUIGAN, Evanston, Ill.

TREATMENT OF TYPHOID INFECTION BY THE NEW DRUG CHLORAMPHENICOL. G. R. BURGIO and L. BAVASTRELLI, Pediatria **58**:853 (Nov.) 1950.

Seventeen children with typhoid were treated with chloramphenicol; 13 others were treated with the di Crastina-Caronia vaccine. Three treated by means of diets served as controls. In the patients treated with chloramphenicol the fever disappeared sooner and sterile blood, urine, and stool cultures were obtained earlier.

HIGGINS, Boston.

ANTIHYALURONIDASE CONTENT OF SERUM OF CHILDREN WITH HEMOLYTIC STREPTOCOCCUS INFECTIONS, OF CHILDREN WITH RHEUMATIC FEVER, AND OF CHILDREN WITH OTHER DISEASES. M. R. H. STOPPELMAN, Nederl. tijdschr. geneesk. **94**:2336 (Aug. 12) 1950.

The antihyaluronidase content of serum was determined by the mucin-clot prevention test. The titer was determined in 705 control children. The mean titer increased with the age. The titer of the serum in children with rheumatic fever was generally high in the acute phase of the disease. A decrease in the titer was seen during recovery, and there was a further decrease during the period of chemoprophylaxis.

In each age subgroup of the control group the values varied greatly. Only 3 of the 11 patients who were acutely ill with rheumatic fever had antihyaluronidase titers which were above the highest value found in other groups. The small number of cases does not warrant definite conclusions. The impression was gained that the determination of the serum antihyaluronidase content may be of diagnostic value in rheumatic fever but will not provide us with diagnostic proof.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

TEST OF RESISTANCE OF VACCINATED AND NONVACCINATED GROUPS OF CHILDREN WITH A HIGHLY CONTAGIOUS EXPOSURE TO TUBERCULOSIS. A. FERRO and S. TARONNA, Clin. pediat. **32**:225 (May) 1950.

During the war years, conditions necessitated the housing of 132 infants in a pavilion of a tuberculosis sanatorium. Fifty-four of the infants had been vaccinated against tuberculosis with Petragnani's anatuberculin (killed tubercle bacilli), while the other 78 had not been vaccinated. Exposure to tuberculosis was largely due to the admission of babies already having a tuberculous infection and to the small quarters and close contact. Eleven infants died of tuberculosis; each of these was in the nonvaccinated group. Of the 23 infants who died of other causes, 18 were from the nonvaccinated group and 5 from the vaccinated group.

This epidemic afforded an unintentional, but quite conclusive, experiment to test the efficacy of Petragnini's anatuberculin in protecting infants against tuberculosis. Even the infants receiving the injections of anatuberculin one month before or during the course of the epidemic received protection.

HIGGINS, Boston.

MODIFICATION OF MANTOUX TEST BY USE OF ANTIHISTAMINIC SYNTHETIC SUBSTANCES. R. ROSSI and A. LOTTINI, Riv. clin. pediat. **49**:667 (Sept.) 1951.

The authors, while practicing Mantoux intradermal injections of tuberculin in association with use of antihistaminic synthetic substances, observed a nearly constant increase of the reaction area in 15 cases and in guinea pigs receiving injections of tuberculin. The authors try to explain such a phenomenon according to the latest interpretations of the Mantoux reaction.

FROM THE AUTHORS' SUMMARY.

DEVELOPMENT AND TREATMENT OF TUBERCULOSIS OF THE CERVICAL LYMPH NODES IN CHILDREN. J. KASTERT and D. HOMMEL, Kinderärztl. Praxis **18**:409 (Sept.-Oct.) 1950.

The authors contend that the portal of entry for the infecting bacilli in tuberculosis of the cervical lymph nodes is in most cases the tonsils, and that the cause is a primary infection with the bovine type of the bacillus introduced through the food. Therapeutically, they practiced tonsillectomy, followed two to three weeks later by radical removal of the cervical lymph nodes.

GLASER, Jerusalem.

Diseases of Blood, Heart and Blood Vessels and Spleen

ELECTROCARDIOGRAPHIC CHANGES IN EXCHANGE TRANSFUSIONS. J. E. GUSTAFSON, J. Pediat. **39**:593 (Nov.) 1951.

Gustafson reports skeletal muscle tremors during replacement transfusions. These were abolished by the administration of calcium. There were no significant electrocardiographic changes.

MACDONALD, Pittsburgh.

CARDIAC ENLARGEMENT OF UNKNOWN ETIOLOGY IN INFANCY AND CHILDHOOD. K. C. LEWIS, J. Pediat. **39**:698 (Dec.) 1951.

The author reports three cases of cardiac enlargement in infants with hypertrophy of the myocardium involving chiefly the left ventricle and endocardial fibrosis. The hypertrophied myocardium showed degenerative changes and signs of myocarditis. Lewis suggests that these myocardial changes are secondary to obliteration of the arterioluminal, arteriosinusoidal, and Thebesian vessels by the severe parietal endocardial fibrosis.

MACDONALD, Pittsburgh.

WAVE CONTOUR IN THE PRECORDIAL LEADS DURING CHILDHOOD. R. W. REYNOLDS, Pediatrics **7**:400 (March) 1951.

The T-wave in the precordial V leads was studied in 187 normal children and young adults in the age range of 2 weeks to 20 years, and in 164 subjects of similar age with cardiovascular disease or with disease or medication capable of affecting the cardiovascular system.

On the basis of this analysis, correlated with a survey of the literature, it is concluded that (*a*) an upright T-wave in Lead V_2 or leads farther to the right should be considered abnormal in children between 2 weeks and 9 years of age until proved otherwise; (*b*) the normal sequence in the direction of the T-wave from V_{1R} to V_6 is from a negative to a positive wave, with transitional forms which may be notched or diphasic (the reversal of this pattern is to be considered abnormal), and (*c*) the presence of unexpected T-wave contours in specific leads at the different ages should be considered as evidence demanding reexamination of the electrocardiogram and of the child for abnormalities.

FROM THE AUTHOR'S SUMMARY.

CHRONIC EOSINOPHILIA DUE TO VISCERAL LARVA MIGRANS. P. C. BEAVER, C. H. SNYDER, G. M. CARRERA, J. H. DENT, and J. W. LAFFERTY, Pediatrics **9**:7 (Jan.) 1952.

Three cases of chronic extreme eosinophilia with granulomatous lesions in the liver were studied. A larval nematode observed in sections of the liver of one patient was identified as Toxocara canis or Toxocara cati. These parasites are common cosmopolitan ascarids of dogs and cats, but the available evidence favors the diagnosis of the former as the invading species.

The term "visceral larva migrans" is proposed for this type of parasitism, known in animals but not previously described in humans. It is related to the better-known cutaneous larva migrans in that both are usually caused by the infective-stage larvae of nematode parasites of other animals. Man, being an abnormal host, either has unfavorable tissue reactions or fails to provide stimulus for the usual tissue migration and development of the parasite. As a result, the larvae remain active for variable periods in such tissues as the liver. Similar, but less severe and less prolonged, reactions occur when the larvae of the normal nematode parasites of man invade the tissues of a hyperimmune person.

Visceral larva migrans is usually a relatively benign disease, characterized chiefly by sustained eosinophilia, pneumonitis, and hepatomegaly. It probably is due both to direct tissue damage by migrating larvae and to allergic responses to their products. Its severity varies with the number of larvae in the tissues and with the immune or allergic state of the infected person.

FROM THE AUTHORS' SUMMARY.

PAROXYSMAL TACHYCARDIA IN INFANTS AND CHILDREN. A. S. NADAS, C. W. DAESCHNER, A. ROTH, and S. L. BLUMENTHAL, Pediatrics **9**:167 (Feb.) 1952.

The authors review 41 cases of paroxysmal tachycardia in infants and children seen within the past 20 years at the Children's Hospital of Boston.

From a detailed analysis of these cases it becomes apparent that a definite entity can be delineated from the tachycardia of the larger group—the disorder occurring in male infants under 4 months of age, who are likely to have congestive failure. These infants may have repeated attacks during the first year of life, but they are extremely unlikely to have paroxysms beyond one year after their first spell. The development of congestive failure in these small infants is related to the longer duration of the tachycardia in them than in children of the older age groups.

The majority of the small-infant group have no organic heart disease accompanying their tachycardia.

Use of digitalis in relatively large doses is the treatment of choice.

FROM THE AUTHORS' SUMMARY.

RELATIONSHIP OF IDIOPATHIC CARDIAC HYPERTROPHY TO FOETAL ENDOCARDITIS. L. E. GLYNN and J. D. L. REINHOLD, Arch. Dis. Childhood **25**:170 (June) 1950.

The phenomenon of fibroelastic hyperplasia of the endocardium in idiopathic cardiac hypertrophy and in so-called fetal (right-sided) endocarditis is discussed. A relationship between these two conditions is suggested largely on the basis of this common finding, and it is illustrated by a fatal case of endocardial fibroelastosis with myocardial hypertrophy in a boy aged 21 months.

KELLY, Milwaukee.

COARCTATION OF THE AORTA (ADULT TYPE) WITH RUPTURE DISTAL TO THE COARCTATION. N. E. FRANCE, B. LEVIN, and B. MCNICHOLL, Arch. Dis. Childhood **25**:175 (June) 1950.

A case of rupture of the aorta distal to coarctation in a boy aged 4 years is reported. The clinical findings and the pathogenesis of rupture of the aorta distal to the coarctation are discussed, and all cases previously reported are reviewed. The importance of the prevention of endarteritis and of its early diagnosis and treatment in such cases is emphasized.

It is concluded that, of the three predisposing factors, mycotic endarteritis plays a much greater part in the causation of rupture distal to the coarctation than in rupture of the ascending aorta proximal to it.

KELLY, Milwaukee.

ANAEMIA IN INFANTS AND CHILDREN. S. CHAUDHURI, Indian J. Pediat. **18**:97 (July) 1951.

Forty-five normal Indian children were studied, with figures showing lower blood values than is normal for European children. The author is of the opinion that, while the blood values are not optimal as compared with those of European children, they are probably to be considered normal for Indian children. Thirty children with clinical evidence of anemia were studied, and of these, 9 were treated by dietary means, the results being tabulated. The anemic group had hemoglobin values from 4 to 7 gm. per 100 cc. and red blood cell counts from 2,200,000 to 4,000,000. Treatment with protein hydrolysate by mouth for two weeks resulted in marked improvement in hemoglobin and red blood cell counts. All children had been on protein-deficient diets, and the authors believe that the usual diet in India precludes the obtaining of blood values comparable to those in European children.

MCGUIGAN, Evanston, Ill.

THROMBASTHENIA IN EARLY INFANCY. E. GLANZMANN, Arch. Kinderh. **141**:191, 1951.

The author describes in detail the case of a 10-day-old male infant who was admitted with severe melena. Occult intestinal bleeding persisted, resulting in severe anemia. This was followed by serious respiratory infections. Each blood transfusion was followed by an intestinal bleeding, and the infant died at the age of 5 months. Autopsy revealed malformations of the intestine and diverticulum of the urinary bladder.

GOTTSTEIN, Chicago.

ENCEPHALITIS IN CHILDHOOD AND SEQUELAE. H. ASPERGER, Wien. klin. Wchnschr. **64**:171 (March 7) 1952.

The paper discusses certain sequelae of various forms of encephalitis in childhood. For details the paper must be consulted.

AMBERG, Rochester, Minn.

CONGENITAL HEART FAILURE: REPORT OF FOUR CASES IN ONE FAMILY. P. ELSHOVE, Nederl. tijdschr. geneesk. **95**:2768 (Sept. 22) 1951.

The author reports on a family in which four cases of congenital vitium cordis occurred. In a brother and sister an open septum ventriculorum was noted, and another brother had stenosis of the aorta. It is very likely that a sister of the mother also had an open septum.

VAN CREVELD, Amsterdam, Netherlands.

EFFECT OF STREPTOMYCIN ON THE BLOOD. A. AFENTAKI, Acta Soc. pediat. hellen. **3**:27 (Jan.-Feb.) 1949.

The total white blood cell count and the differential count were examined at frequent intervals in 18 children with tuberculous meningitis who were under treatment with streptomycin. In 15 children there was a steady increase in the eosinophiles, an average count of 20% being attained at the third or fourth month of treatment. The remaining children, who did not show such an eosinophile response, were seriously ill. It is suggested that eosinophilia may indicate a favorable response to treatment with streptomycin.

DOXIADIS, Sheffield, England.

Diseases of Nose, Throat, and Ear

HEARING AIDS FOR YOUNG CHILDREN. J. L. BANGS, and T. E. BANGS, A. M. A. Arch. Otolaryng. **55**:528 (May) 1952.

In testing children from 18 months to 5 years of age who shy away from auditory equipment, a French phone is used. The difficulty in obtaining a pure-tone audiogram at this age is discussed. The development of awareness of sound is the first step in auditory training. It must proceed slowly enough so that rapport is maintained. The details of the child's self-adjustment to his hearing aid are discussed.

KIMBALL, Evanston, Ill.

STURGE-WEBER DISEASE AS AN OTOLARYNGOLOGICAL PROBLEM. R. J. MCMAHON, A. M. A. Arch. Otolaryng. **54**:542 (Nov.) 1951.

The pathogenesis of Sturge-Weber disease (nevoid amentia) appears to be a hemangiomatous formation in the layer of mesenchyme directly bordering on the ectoderm, from which are derived the skin in the cephalic region; the mucous membrane of the mouth, nose and throat; the choroid coat of the eye, and the leptomeninges enveloping the brain. Various methods of treatment are described in the literature. The following modalities are most frequently mentioned as therapeutic agents of choice: (1) radiation, including x-rays, radium, and radon; (2) sclerosing solutions (sodium morrhuate); (3) solid carbon dioxide, and (4) direct ligation, excision, or coagulation.

McMahon describes the case of a 9-week-old infant who had had small multiple hemangiomas involving, on the right side, the eyelid, forehead, external ear, scalp, neck, and mucous membranes of the mouth and pharynx since birth. These lesions were increasing in size, and for the past three weeks respiratory distress had been present and was getting progressively worse.

A lateral roentgenogram of the neck suggested a subglottic area of stenosis. Direct laryngoscopy and bronchoscopy demonstrated a subglottic stenosis. Roentgenograms of the skull revealed poorly defined intracranial calcifications in the posterior parietal region on the left side.

Therapy with humidified oxygen and subsequent tracheotomy relieved the respiratory distress. In the light of the intracranial involvement, the prognosis was thought to be poor. The immediate concern was the patency of the airways. It was deemed unwise to remove a biopsy specimen from the subglottic area of stenosis because of the extreme danger of uncontrollable hemorrhage. Needle implantation in this area would be as dangerous as removal of a specimen for biopsy, while application of a radium plaque or of solid carbon dioxide to the stenotic area was mechanically impossible in a patient of this age. With the area of stenosis overlying the vertebral column and being relatively close to the base of the skull, it was thought that cross firing of multiple x-ray ports might endanger nearby growth centers. The patient is to be followed at six-month intervals and subsequent treatments given in the light of survival.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

INTRAVENOUS PROCAINE FOLLOWING TONSILLECTOMY. KENNETH SOMERS, Ann. Otol. Rhin. & Laryng. **60**:175 (March) 1951.

Inasmuch as good results have been reported when a dilute solution of procaine is given intravenously for the treatment of a variety of traumatic and painful conditions, Somers utilized this preparation in an attempt to relieve post-tonsillectomy pain. A discussion of the mode of action and probable safe therapeutic intravenous dosage of procaine is presented.

Forty-one patients were given intravenous injections of procaine hydrochloride on the day following tonsillectomy. The first group, of 18 patients, received 10 cc. of a 1% solution, while the second group, of 20 patients, received 10 cc. of a 2% solution and a third group, of 3 patients, were given 20 cc. of a 2% solution. All injections were administered within a five-minute period. In the first group analgesia of the tonsillar fossae lasted an average of 2 hours, while patients in the second group experienced analgesia for about 4 hours and those in the third group for 9½ hours. A fairly high blood level of procaine was demonstrated in five of the patients 15 minutes after the intravenous injection.

Unpleasant symptoms experienced by patients during injection are believed to preclude the possibility that this form of therapy will become of value in routine post-tonsillectomy care.

STEELE, Kansas City, Kan. [A. M. A. Arch. Otolaryng.].

MEASURING THE SEVERITY OF STUTTERING. DON LEWIS and DOROTHY SHERMAN, J. Speech & Hearing Disorders **16**:320 (Dec.) 1951.

The severity of stuttering was judged by 30 elementary psychology students on 240 nine-second samples of stuttering speech. Dividing the range of severity into eight intervals, three "expert" judges selected 96 samples with small Q-values to cover the entire range of severity. These 96 samples were presented to 106 elementary psychology students. Scale values obtained from judgments by Group 1 were compared with judgments from Group 2. Reliability was high.

PALMER, Wichita, Kan. [A. M. A. Arch. Otolaryng.].

CONSIDERATION OF THIAMIN SUPPLEMENT IN PREVENTION OF STUTTERING IN PRESCHOOL CHILDREN. L. L. HALE, J. Speech & Hearing Disorders **16**:327 (Dec.) 1951.

Ten milligrams of thiamine hydrochloride was administered three times daily to stutterers of preschool age and a placebo to a control group of preschool stutterers. After one month, treatment was reversed and observation continued for another month. Neither the clinicians nor the parents knew which preparation the child was receiving. Observable speech improvement occurred in 55% of all patients treated with thiamine. Improvement occurred primarily in the first two weeks of treatment. Of the 2- and 3-year-old children, 80% made improvement; of the 4-year-old children, 50%. Hale believes that thiamine may be helpful in the prevention of stuttering in preschool children.

PALMER, Wichita, Kan. [A. M. A. Arch. Otolaryng.].

ACUTE LARYNGOTRACHEOBRONCHITIS. F. G. FOLKEN, Minnesota Med. **35**:336 (April) 1952.

The author reviews the subject of acute laryngotracheobronchitis. In the differential diagnosis laryngeal diphtheria must be ruled out. The treatment consists of the use of moisture, preferably cold humidity, antibiotics, and oxygen. Antihistamine drugs are contraindicated. Atropine and codeine should not be used, since they may increase the viscosity of the sputum. Hydration of the patient is important. If the dyspnea increases in spite of these measures, and if laryngeal obstruction becomes severer, tracheotomy is indicated. The high postoperative mortality can be avoided with adequate postoperative care.

STUSSER, Minneapolis.

NASAL TRIAD, NASAL ALLERGY, AND DEAFNESS. A. R. MILLER, Northwest. Med. **51**:302 (April) 1952.

It is not sufficiently recognized by members of the medical profession at large that a high percentage of deafness is caused by increased nasopharyngeal pressure. This increase of pressure is brought about by sneezing and blowing the nose when there is decreased nasal space for secretions. Three of the most important causes of decrease in nasal space are (1) adenoids; (2) deviation of the nasal septum, with compensatory hypertrophy of the turbinates, and (3) nasal allergy, with edematous swelling of the mucosa and polypoid formation of all degrees.

The author emphasizes the importance of early correction of the causes of decreased nasal space by the removal of adenoids, the correction of the deviation of the nasal septum, and the treatment of nasal allergy with the removal of polyps, even if occurring early in childhood. The author's conclusions are well described on the basis of the physiological mechanisms involved, and the anatomical pathology is well illustrated by diagrams and drawings.

DOCTOR, Seattle.

EARACHE. E. J. SMITH, Canad. M. A. J. **66**:234 (March) 1952.

Almost all possible causes of earache are discussed briefly. The author stresses the point that severity of the earache is not a good indication of the severity of the disease and that earache may be an early symptom of serious disease of the upper respiratory tract or gastrointestinal tract.

MCGUIGAN, Evanston, Ill.

PERACUTE PHLEGMONOUS EDEMATOUS EPIGLOSSITIS. C. GASSER, Schweiz. med. Wchnschr. **82**:379 (April 12) 1952.

The ages of the 25 (26?) patients varied from 15 months to 7½ years. No special tendency to allergy was noted. The children were sent to the hospital with various diagnoses, such as laryngeal diphtheria, pseudocroup (laryngismus stridulus), pharyngeal abscess, and foreign body. Clinically important is a rapidly progressing dyspnea without hoarseness, without the cough of pseudocroup, without exudations in the throat, and without pulmonary involvement. The swollen epiglottis is readily palpable. The prognosis depends upon the early diagnosis, when it may be possible to avoid tracheotomy by energetic antibiotic treatment, with stimulation of circulation. Thus, the mortality could be reduced from 80 to 20%. Occasionally severe complications occur.

AMBERG, Rochester, Minn.

VOCAL AUDIOMETRY (PHONOGRAPHY) IN SCHOOL CHILDREN. C. A. BAUZA, and A. MARTINEZ, Arch. pediat. Uruguay **20**:526 (Aug.) 1949.

The foundation and evolution of phonographic speech-hearing testing are summarized. The Servicio de Sanidad Escolar (School Health Service) of the Consejo del Niño of Uruguay uses the Western Electric 4 C A audiometer for the early detection of impairment of air-conduction hearing among school children. The audiometer is described, and the various steps involved in the testing procedure which was used in the schools of Montevideo are given. The method is easy and allows the testing of groups of 40 children; the test is easy to perform, and the scoring offers no difficulty. The sound being uniform, the test can be repeated, and it is possible to find out whether the hearing has improved after therapy or not. The various terms used to express hearing impairment are defined.

FROM THE AUTHORS' SUMMARY.

CYTOLOGICAL STUDIES OF SPUTUM AND BRONCHIAL SWABS. P. LOPES CARDOZO and C. A. L. JANSSEN, Nederl. tijdschr. geneesk. **94**:2318 (Aug. 12) 1950.

Sputum or bronchial swabs were studied in 130 patients. The Giemsa stain was used throughout. The normal cells present in sputum and swabs, as well as the aspects of various tumor cells, are described. Of 33 cases of bronchial tumors, diagnosis was made by cytological examination in 31. In 26 of these 31 cases the diagnosis was confirmed by pathoanatomical examination. In three of these cases neither the sputum nor the bronchial swab revealed tumor cells. The method is time-consuming.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

LOCALIZED HYPERTROPHIC EMPHYSEMA. R. R. SHAW, Pediatrics **9**:220 (Feb.) 1952.

Localized emphysema involving a segment of a lobe or a whole lobe which is not associated with an aspirated foreign body or the tenacious mucus of an infection of the upper respiratory tract is a rare condition which has received little attention in the literature. It is important that it be diagnosed early in infancy, since early surgical removal of the involved pulmonary tissue will improve the infant's respiration and prevent deformity of the chest. This condition usually makes itself known within the first month of life and is characterized by a wheezing type of respiration with transient periods of cyanosis. There may also be some slight in-pulling of the chondral margins upon inspiration. The roentgenographic findings are those of a translucency involving perhaps an entire hemithorax, with displacement of the mediastinum away from the involved side. The absence of breath sounds over the area which shows the greatest translucency in the roentgenogram is the key to the diagnosis. Surgical removal of the involved segment is well tolerated by the infant, and as a rule, the respiratory capacity of the child is immediately improved. Two cases are reported to illustrate this clinical entity. The probable mechanical factors in the condition are discussed.

FROM THE AUTHOR'S SUMMARY.

ORIGIN OF LUNG CYSTS IN CHILDHOOD. D. J. CONWAY, Arch. Dis. Childhood **26**:528 (Dec.) 1951.

Cysts in the child's lung may be congenital or acquired. Very few have been recorded in stillborn or newborn infants, but it has been generally assumed that most cysts are due to congenital malformation.

A number of cases of lung cysts, observed over many years, are reviewed, and the etiology of the cysts is discussed.

The conclusion is reached that most lung cysts are acquired as a result of bronchial inflammation and obstruction and that very few are truly congenital.

KELLY, Milwaukee.

LOCALIZATION OF LOBAR PNEUMONIA IN CHILDHOOD. S. ENGEL, Schweiz. med. Wchnschr. **82**:403 (April 12) 1952.

Various factors are described which favor the development of pneumonia in certain parts of the lung, particularly in the upper lobe of the right lung.

AMBERG, Rochester, Minn.

CHRONIC BRONCHITIS IN THE CHILD. H. WISSLER, Schweiz. med. Wchnschr. **82**:413 (April 12) 1952.

The paper is concerned mainly with cylindrical dilatations of the bronchi in cases of chronic bronchitis. It is stated that in most cases the disease of the bronchi is associated with maxillary sinusitis. Frequently, cylindrical bronchiectases of parts of the lung are seen. They are regarded as secondary manifestations. In general, the prognosis is good. The principles of therapy are outlined.

AMBERG, Rochester, Minn.

BRONCHIECTASES WITH ATYPICAL LOCALIZATION SIMULATING A CAVITY, IN A 10-YEAR-OLD CHILD. R. NEUMANN, Pediat. listy **6**:344, 1950.

A case of bronchiectasis localized in the upper lobe of the left lung in a 10-year-old child is described.

FROM THE AUTHOR'S SUMMARY.

SIMULTANEOUS VISUALIZATION OF POSTERIOR AND ANTERIOR MEDIASTINUM AFTER INSUFFLATION OF THE PERIDURAL SPACE: TRIDIMENSIONAL TOMOGRAPHIC STUDY. G. SANSONE and A. DE MAESTRI, Acta paediat. **41**:101 (March) 1952.

From personal experience, the authors state that the method of gaseous insufflation of the peridural space through the intrarachidian extradural way is an ideal procedure in pediatrics, which allows a simultaneous and sharp visualization both of the anterior and of the posterior mediastinum. It is easy, safe, and well tolerated by children. In association with tomography (in anteroposterior, lateral, and axial transverse projections) this method gives the possibility of very interesting tridimensional pictures. The authors foresee, therefore, a wide application of this technique in the roentgenological diagnosis of morbid conditions of the mediastinum. In the study of various congenital heart diseases it will represent, in association with other techniques, an invaluable method of investigation.

FROM THE AUTHORS' SUMMARY.

VASCULAR ANOMALY CAUSING TRACHEAL STRIDOR AND PAROXYSMAL SUFFOCATION ATTACKS IN INFANTS. ROLF KOSTMAN, Nord. med. **40**:2153 (Nov. 19) 1948.

The case is reported of a 2-month-old girl who had displayed cyanosis and attacks of increasing respiratory distress and suffocation since the age of one month. Clinically, the stridor was found to be caused by a tracheal compression in and below the collarbone. At operation it could be ascertained that the trachea was pressed flat in that vena anonyma sinistra and arteria anonyma dextra crossed over the front of the trachea, in a diagonal from the left below to the right above. No other condition explaining the tracheal compression was observed. The two vessels were ligated and extirpated. The patient survived the operation for only a few hours. Postmortem examination showed that the trachea was pressed flat from the clavicle to the bifurcation.

WALLGREN, Stockholm, Sweden.

PRIMARY ATYPICAL VIRUS PNEUMONIA IN CHILDREN. D. P. R. KEIZER, Maandschr. kindergeneesk. **17**:172, 1949.

During an epidemic of virus pneumonia beginning before the "flu," 41 cases were studied. The clinical course, the paucity of physical signs, the help of x-rays, and the laboratory findings are discussed. The cold-agglutination titer is not specific for virus pneumonia, but it may be of tremendous help after liver and some other diseases are excluded. It is important to follow the cold-agglutination titer for the diagnosis and prognosis. Even with a mortality rate of zero, the chronic course and the risk of dangerous complications make this disease rather a serious one for children. Anemia, anorexia, chronic diarrhea, clouding of the maxillary sinus, acute mastoiditis, pleurisy, endomyopericarditis, hepatitis, acute nephritis, benign reticulosis, arthritis, encephalopathy, exanthema (Stevens-Johnson syndrome), and acute hypoadrenalism formed the complications seen in the cases studied.

Sulfonamides and penicillin served only to combat bacterial secondary infections, with a risk of the sulfonamides causing serious anemia. The use of gamma-globulins in a dose of 0.2 cc. per kilogram of body weight helped in serious cases, without any guarantee, however, against relapse and reinfection.

Infections in the family were not infrequent, without there being a chance to study the incubation period. In none of his cases did the author find nonspecific reactions for syphilis.

FROM THE AUTHOR'S SUMMARY.

Diseases of Ductless Glands; Endocrinology

EFFECT OF FRACTURES UPON URINARY ELECTROLYTES IN NON-ADRENALECTOMIZED RATS AND IN ADRENALECTOMIZED RATS TREATED WITH ADRENAL CORTEX EXTRACT. D. J. INGLE, R. C. MEEKS and K. E. THOMAS, Endocrinology **49**:703 (Dec.) 1951.

One of the characteristic metabolic responses of man and of laboratory animals to injury is a temporary decrease in the urinary excretion of sodium and chloride. Since certain of the hormones of the adrenal cortex cause the retention of these ions and since the secretory activity of the adrenal cortex is increased during any type of stress, the authors tested the hypothesis that the retention of sodium and chloride following fractures in the rat is caused by an increase in the secretion of cortical hormones. Adrenalectomized rats treated with a constant intake of adrenal-cortex extract were found to show a striking temporary reduction in the urinary sodium and chloride following multiple fractures of the back legs, just as did nonadrenalectomized rats.

It was concluded that the observed responses to injury were not mediated by a change in the secretory activity of the adrenal cortex.

JACOBSEN, Buffalo.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

TRENDS IN THE MANAGEMENT OF APPENDICITIS IN CHILDREN. P. F. FOX, Illinois M. J. **100**:241 (Oct.) 1951.

During the four-year period from Jan. 1, 1946, to Jan. 1, 1950, a total of 178 patients with acute appendicitis were treated at Children's Memorial Hospital, Chicago. The mortality rate was 1.6%. There were no deaths among 110 patients who had acute and gangrenous appendicitis. In the 1921-1935 series, however, there were 297 comparable cases, with three deaths, or a mortality rate of 1%. Among the 68 patients admitted with appendicitis and perforation during the period from 1946 to 1950 there were three deaths, a mortality rate of 4.4%. This shows a substantial decrease in the mortality rate over that of the 1921-1935 series, in which it was 11.8%. The more favorable outcome in the 1946-1950 series is believed to be principally the result of the use of chemotherapeutic and antibiotic drugs.

FROM THE AUTHOR'S SUMMARY.

GASTRIC DIVERTICULA IN INFANCY. G. L. OGUR, and A. J. KOLARSICK, J. Pediat. **39**:723 (Dec.) 1951.

Gastric diverticula are rare in the pediatric age group; the authors could find only six previously reported cases. They report a gastric diverticulum, with intussusception into the stomach causing gangrene, perforation, and peritonitis. This is the first case of gastric diverticulum reported in a newborn infant and is the first reported case with these complications, either in an adult or in a child. The second case reported is one of an acquired diverticulum secondary to unrelieved pyloric stenosis.

MACDONALD, Pittsburgh.

DUODENAL OBSTRUCTION: REPORT OF TWO CASES. M. JACCOTTET, Schweiz. med. Wchnschr. **82**:385 (April 12) 1952.

An infant with duodenal obstruction was subjected to a gastroenterostomy. The condition at the time of operation prevented further exploration, so that the seat of the obstruction was not determined. In a second infant a band arising from the mesentery constricted the jejunum adjoining the duodenum. The third portion of the duodenum was adherent to the cecum and the ascending colon. The band was sectioned and the duodenum freed from the adhesions. Both infants did well.

AMBERG, Rochester, Minn.

TREATMENT OF CELIAC DISEASE WITH CORTICOTROPIN AND CORTISONE. J. UGLAND, L. WENNEVOLD, and L. SALOMONSEN, Schweiz. med. Wchnschr. **82**:420 (April 12) 1952.

Four patients with celiac disease were benefited by treatment with corticotropin or cortisone. There was improvement in the general condition, appetite, aspect and fat content of the stool, sideropenia, anemia and hypoproteinemia, and response to the sugar tolerance test. Osteoporosis, development of ossification centers, and characteristic x-ray changes in the small intestine were not influenced.

AMBERG, Rochester, Minn.

CONGENITAL CYSTIC MALFORMATIONS OF THE BILE DUCT. H. GARCES, M. NEIRA, and A. GUZMAN, Rev. chilena pediat. **23**:1 (Jan.) 1952.

The authors report three cases of congenital cystic malformation of the common bile duct in infancy, emphasizing the importance of precocious diagnosis of this condition in order that surgical treatment may be performed opportunely, before severe complications develop. In the first case an 8-month-old infant who had presented jaundice since the age of 15 days died of biliary cirrhosis of the liver; in the second a 3-month-old infant died of biliary peritonitis following rupture of the cyst, and in the third a girl 1 year 4 months of age with an uncomplicated congenital cystic malformation of the common bile duct underwent choledochoduodenostomy, with complete recovery.

FROM THE AUTHORS' SUMMARY.

DUODENAL DIVERTICULUM WITH OCCLUSION. H. WEYERS, Arch. Kinderh. **143**:179, 1951.

The case of a 1-year-old boy who showed the signs of hypertrophic pyloric stenosis during infancy is reported. X-ray studies revealed an infrapyloric-duodenal stenosis encroaching on the descending duodenal segment. Exploration showed extensive adhesions, which were separated, with obvious restoration of normal caudal filling. However, after operation a stenosis developed and led to fatal outcome within a few days. Necropsy revealed a cherry-sized duodenal diverticulum and a stenosing transversal band which had resulted in intermittent occlusion, back pressure, and enormous dilatation of the proximal loop.

GOTTSTEIN, Chicago.

METHIONINE FOR LIVER FUNCTION TEST. K. SCHREIER and H. SCHÖNSEE, Deutsche med. Wchnschr. **77**:418 (April 4) 1952.

The excretion of methionine in the urine after its oral administration as *dl*-methionine was quantitated by a colorimetric method, which is described. The dose in 48 children without hepatic disorder, aged 6 to 15¾ years, was 0.2 gm. per kilogram of body weight. Ten healthy adults received 10 gm. each. The urine for the 24 hours following the administration was collected. Children eliminated between 6 and 12% of the methionine; adults, between 11.5 and 13%. In

younger children an excretion of more than 15%, and in adults an excretion over 19%, is regarded as surely pathological. Adults with hepatic disease may excrete more than 30%: in 8 of 15 determinations in children, a value exceeding 15% was obtained. In cases of nephritis the values were unusually low. The microbiological estimation showed that very little *l*-methionine was excreted.

AMBERG, Rochester, Minn.

ORAL STREPTOMYCIN THERAPY OF GASTROINTESTINAL INTOXICATION. R. ROTT, Kinderärztl. Praxis **18**:219 (No. 5/6) 1950.

Twenty children with severe gastrointestinal disturbances with intoxication, dehydration, and acidosis were treated with oral administration of 0.5 gm. of streptomycin in water. The children received between 2 and 3 gm. over a period of four to five days. Bacteriological examination revealed Escherichia coli, Proteus vulgaris, and enterococci. The stools were found to be sterile in nine cases after streptomycin therapy; in the other cases the number of colonies was greatly reduced. The author observed a considerably speedier clinical recovery than in patients who did not receive streptomycin.

GLASER, Jerusalem.

NECROTIZING ENTERITIS IN INFANTS AND YOUNG CHILDREN. H. HARTIG, Ztschr. Kinderh. **68**:32 (No. 1) 1950.

Seven cases of acute intestinal disturbances are described. Five of the patients died, and necrotic lesions of the intestine were found. The cause of the necrosis may be a specific bacterium, a local allergic reaction (Shwartzman phenomenon) to bacterial infection, or toxic effects upon the blood vessels or their nerves. The necrosis does not seem to occur all at once, as healed and fresh lesions could be found; it occurs in various segments of the bowel. Necrotic foci may occur in other organs as well.

GLASER, Jerusalem.

PYLORIC STENOSIS ON THE BASIS OF ABERRANT VESSELS. V. TOSOVSKY, A. PISKACOVA, and J. ZLENKA, Pediat. listy **7**:44 (Jan.) 1952.

A case of congenital pyloric stenosis occurring on the basis of aberrant vessels in a 2½-month-old infant is described.

FROM THE AUTHORS' SUMMARY.

Nervous Diseases

TWO TYPES OF WILSON'S DISEASE: HEPATO-LENTICULAR DEGENERATION. H. PIERSON. J. Neuropath. & Exper. Neurol. **11**:19, 1952.

A survey of the literature indicates that three types of Wilson's disease can be recognized: 1. The hepatolenticular type, in which both hepatic and cerebral lesions are present. It is the form most commonly encountered in the literature. 2. The hepatic type, in which cerebral lesions are absent. It is the so-called abdominal type of Silaon and Kehrer, a type generally observed in siblings affected with typical Wilson's disease. 3. The lenticular type, in which the liver is apparently not involved.

Two cases of the disease, affecting two brothers, representing the first two types of Wilson's disease, are reported.

In one case, in which the liver alone disclosed pathologic changes, the clinical course was comparatively mild and chronic; neurologic and mental symptoms pointed to basal-ganglion disease, which was classified as progressive lenticular degeneration (Wilson's disease).

In the other case, in which both the brain and the liver were affected, the clinical course took an acute and violent form. At the age of 14, there was apparent severe damage to the liver with attacks of hematemesis. The subsequent course of the disease disabled the patient, as there developed rapidly severe neurologic and mental symptoms, such as complete mutism, rigidity of the whole body, paralysis, and mental disturbances, necessitating permanent care in the state hospital and leading to an early death.

Gross and microscopic observations at autopsy in both siblings are reported, with particular emphasis on changes in the brain.

The author points out that this disease has a familial character, that it may have several variants, and that the theory that the liver is first affected and the lenticular lesions follow as a result of the action of the pathogenic agent is now generally accepted. Pierson discusses the relation between severe chronic alcoholism and lowered resistance in the offspring, suggesting the possibility that the resulting organic deterioration of the basal ganglia may serve as a suitable soil for the, as yet unknown, causative agent in hepatolenticular degeneration.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

INTRACRANIAL MALIGNANT NEOPLASM WITH ONSET BEFORE BIRTH. R. L. THIELE and M. J. DIMMICK, J. Pediat. **39**:611 (Nov.) 1951.

A case of glioma in a newborn infant, manifest by congenital hydrocephalus, is reported.

MACDONALD, Pittsburgh.

INTRANASAL MENINGOCELE. T. E. BEYER, J. R. BLAIR, and W. R. LIPSCOMB, Laryngoscope **61**:917 (Sept.) 1951.

Meningocele is rare. It results from herniation of the pia and arachnoid through a dehiscence in the skull. Intranasal meningoceles herniate through a dehiscence in the cribriform plate. They may be confused with polypi. The treatment of choice is ligation of the meningocele by means of the radical transfrontoethmoid operation or by craniotomy. Two cases are presented.

HITSCHLER, Philadelphia [A. M. A. Arch. Otolaryng.].

PSEUDOMONAS MENINGITIS IN AN INFANT SUCCESSFULLY TREATED WITH NEOMYCIN. S. DITKOWSKY, A. GOLDMAN, and M. GOLDIN, Pediatrics **9**:101 (Jan.) 1952.

A brief review of the literature of Pseudomonas aeruginosa meningitis is given, together with a discussion of the mortality rate of the disease and its present-day therapy. Despite the favorable results of recent studies on the in vitro sensitivity of the organism to neomycin, the clinical use of this drug has been limited because of the reported toxic effects of its parenteral use. A case of *Ps. aeruginosa* meningitis occurring in an infant after the surgical repair of a meningomyelocele is presented. This infection had failed to respond to penicillin and aureomycin therapy, but the organism was found sensitive in vitro to 3.12 γ per cubic centimeter of neomycin. Intramuscular therapy with 1,700 units of neomycin every four hours for nine days resulted in a rapid cure. When seen eight months later, the child showed no evidence of a recurrence of the disease process.

FROM THE AUTHORS' SUMMARY.

BRAIN ABSCESS ASSOCIATED WITH CONGENITAL HEART DISEASE. R. GLUCK, J. W. HALL, and L. D. STEVENSON, Pediatrics **9**:192 (Feb.) 1952.

Forty-one cases of brain abscess associated with congenital heart disease are summarized from the literature, and three additional cases are reported. The clinical signs and symptoms of brain abscess are discussed, with special emphasis on the need for early surgical intervention. The occurrence of persistent headache or lethargy in a patient with congenital heart disease should be investigated by means of a spinal tap, an electroencephalogram, and cranial air studies before excluding the diagnosis of brain abscess. The theory that an area of infarction in the brain precedes the development of an abscess is presented, and a number of possible explanations are offered for the development of the infarction, such as paradoxical emboli, emboli from the lungs reaching the brain through the systemic arterial circulation by way of the pulmonary vein, left auricle, and left ventricle, emboli from the lungs through the spinal veins, and, finally, thrombosis of the cerebral arteries. The tendency to systemic and pulmonary thromboses in cases of congenital heart disease is best explained on the basis of decreased flow of blood, due to polycythemia or decreased pulmonary blood flow.

FROM THE AUTHOR'S SUMMARY.

CONGENITAL HEMIATROPHY OF THE BRAIN. L. CROME, Arch. Dis. Childhood. **26**:614 (Dec.) 1951.

The literature relating to hemiatrophy of the brain is reviewed and its possible etiology discussed. A case of hemiatrophy is reported and it is suggested that it followed birth injury associated with prematurity. The nosological position of progressive sclerosing hemiatrophy of Schob is also discussed.

KELLY, Milwaukee.

PNEUMOCOCCAL MENINGITIS WITH SUBDURAL EFFUSIONS. E. KAHN and M. H. SHNIER, South African M. J. **26**:212 (March 15) 1952.

The authors present two cases of subdural effusion complicating pneumococcic meningitis in infants. The condition is reported to have been found in 20% of 43 cases of meningitis in children under 2 years of age, more commonly in severe cases of influenzal or pneumococcic meningitis.

McGUIGAN, Evanston, Ill.

CRITICAL STUDY OF BIOLOGIC TESTS IN DIAGNOSIS OF SPASMOPHILIA IN THE CHILD: III. TEST FOR RESISTANCE TO INDUCED HYPERCALCEMIA. P. GIRARDET and H. ZELLWEGER, Helvet. paediat. acta **6**:459 (Nov.) 1951.

Füngeld's test of resistance to the induction of hypercalcemia has been shown to give positive results in 22 of 32 cases of normocalcemic tetany arising from various causes. This test is certainly less sensitive than the diagnostic tests for latent tetany which have been used up to the present. It gives no indication as to treatment and no information as to the cause of the disease.

FROM THE AUTHORS' SUMMARY.

SWALLOWING APNEA. H. WILLI and F. LÜTHY, Schweiz. med. Wchnschr. **82**:397 (April 12) 1952.

A girl baby was admitted with a lumbosacral meningocele. On the fourth day of life the newborn infant suddenly collapsed when drinking. The attacks repeated themselves always during feeding. Apnea of long duration, spasms, and loss of consciousness occurred, and the color became bluish-black. After one to three minutes of apnea, gasping respiration set in, with slow transition to normal respiration. In the third month the meningocele, which had been emptied repeatedly, did not increase further. At the end of the third month pneumonia supervened, with resulting death. Histological examination of the medulla oblongata revealed destruction of the substantia reticularis, that is, in the region of the respiratory center, with residua of a hemorrhage. It is assumed that, owing to this defect, the respiratory center could be readily inhibited by the activity of the (adjacent) swallowing center.

AMBERG, Rochester, Minn.

OBSERVATIONS WITH REGARD TO THE GLUCOSE CONTENT OF CEREBROSPINAL FLUID. R. DUBOIS, Schweiz. med. Wchnschr. **82**:401 (April 12) 1952.

After a fast of 12 hours, the glucose contents of the blood and the spinal fluid were quantitated, and the amount of glucose in the blood was divided by the amount in the spinal fluid. In 20 infants without any involvement of the nervous system, this quotient varied from 1.16 to 1.86, with an average of 1.46, the majority of the determinations being close to this average. In a case of brain tumor, the quotients in seven determinations ranged from 1.12 to 1.34; once it was 2.0. In one instance, a case of congenital communicating hydrocephalus, the amount of glucose in the fluid obtained by spinal puncture and that obtained from a ventricle were the same. No glycolysis occurred after incubation for as much as 24 hours at 37 C. (98.6 F.). As is to be expected, the quotient is greatly increased in cases of tuberculous meningitis. Here, also, no glycolysis was seen. Under successful streptomycin treatment, the sugar of the fluid increased with a decrease in the quotient. Sometimes a reversal preceded a relapse by some days or weeks. During the first weeks of treatment, the glucose of the ventricular fluid exceeded that of the spinal-puncture fluid obtained at the same time. With improvement, this difference disappeared.

AMBERG, Rochester, Minn.

CONGENITAL CEREBRAL PATHOLOGY DUE TO MENINGEAL-CEREBRAL HEMORRHAGE. P. BRUSA, Minerva pediat. 4:4 (Jan. 15) 1952.

Three infants under one month of age presented symptoms of brain injury, proved by lumbar puncture to be due to cerebral hemorrhage. The infants died three to six months later; at autopsy, cortical atrophy and hydrocephalus were found.

HIGGINS, Boston.

STREPTOMYCIN-RESISTANT BACTERIAL FLORA IN TUBERCULOUS MENINGITIS AND THE RELATION TO RECURRENCE OF THE MENINGITIS. A. MURATORE, Riv. clin. pediat. 48:291 (March) 1950.

The author, having observed that purulent septic meningitis complicating tuberculous meningitis treated with streptomycin is often brought about by streptomycin-resistant bacteria, has studied streptomycin resistance in vitro of the bacterial flora of tuberculous meningitis, noting the presence of bacteria resistant to large doses of antibiotic, both in the wards and in the pharynx of patients and staff members.

The patients affected by tuberculous meningitis at the beginning of streptomycin treatment present natural streptomycin resistance (up to 15γ); during the course of the therapy the flora becomes mostly and definitely resistant (above 50γ) also during the first month of treatment, retaining such characteristic even after use of the antibiotic has been suspended for many months.

The increase of streptomycin resistance depending on the presence of the antibiotic, as is shown only by patients under treatment, causes the patients themselves to be, evidently, the center of culture and of dispersion of such resistant bacteria, spreading them in the surroundings and contaminating those who live with them.

For the same reason, the patients being under streptomycin treatment, every supervening infection is generally counterattacked by streptomycin-resistant bacteria, which the author has confirmed with experiments of resistance (in vitro) of 23 strains isolated from septic complications supervening in tuberculous meningitis (20 from purulent meningitis, 2 from abscesses, 1 from pustules). Of the 23 strains, 18 were resistent to any dose tried (1,000); the other 5 offering nearly no resistance had been isolated from the ventricle of patients who had been submitted to skull trephining and who had received ventricular therapy only in very small doses.

Resistance to penicillin and co-streptosil of the same strains has also been determined, in order to learn how much one can rely on such drugs in the treatment of tuberculous meningitis.

More than penicillin, sulfamides have proved most efficient; in fact of the 23 strains, while only 6 were sensible to any dose of penicillin, on the contrary nearly all were inhibited in their development by co-streptosil in therapeutic doses except for 2 which were sensible to penicillin.

FROM THE AUTHOR'S SUMMARY.

MICROCEPHALIA. LORENZO BIANCHI and SERGIO LEVI, Riv. clin. pediat. 48:625 (Oct.) 1950.

The brain of a one-year-old girl with microcephaly was studied. The reduction of the dimensions of the neurocranium is attributed to the reduction of the encephalic mass; the dependence of the skull size on that of the encephalon, and not the reverse, is now definitely established, thanks to the studies of many authors. It has also been ascertained that the brain is the part of the encephalon presenting most alterations, the other parts undergoing modifications as a consequence of cerebral alterations; the present study deals exclusively with the cerebral cortex. The gyri and sulci of the brain at the examination showed more simple and rudimentary dispositions than those of normal subjects. Characteristics proper to the normal human as well as aspects reminding us of the sulci are found in the skull of monkeys. This is true in many other cases, as documented in literature, and is easily explained if it is remembered that the brain, constructed on a common order, shows differences only in degree, not in quality. Therefore, a human brain with a less extended cerebral cortex must necessarily present monkey-like aspects, though this in no way proves the possibility of a return to an atavistic character.

The cerebral cortex in this case did not show any profound structural qualitative alterations. Many of its cells had normal aspects, while others had abnormal aspects and arrests in development. In any event, the principal cortical areas were to be recognized by their essential struc-

tural characters. A remarkable diminution in the number of cells throughout the cortex, particularly visible in the granular and supergranular strata, was in progress and was demonstrated by relative measures.

Pathogenetic causes, the presumably determining causes of microcephaly, are mentioned and discussed; in the case reported the cause is ascribed to an indeterminate arrest of development which prevented the normal process of cell multiplication. Therefore, though many elements retained their normal formative activity (inasmuch as the cortex in examination showed no fetal aspect), a large reduction in the total quantity of cerebral cortex ensued, making it impossible for the cortex to expand as much as its age would require.

FROM THE AUTHORS' SUMMARY.

PERMEABILITY OF THE MENINGES OF THE CHILD BY PENICILLIN ADMINISTERED INTRAMUSCULARLY. CARMEN AGUILO and FUAD GERMANY, Rev. chilena pediat. **23**:1 (Jan.) 1952.

A comparative study was undertaken of the permeability of normal meninges to penicillin in children of different ages. The infants were divided into the following groups: newborn infants under 1 day old, newborn infants between 5 and 7 days old, infants in the first half-year of life, and infants in the second half-year of life. All received a single intramuscular injection of 35,000 units of penicillin per kilogram of body weight. Penicillin concentration in the cerebrospinal fluid was determined 15, 90, and 240 minutes after injection. The authors also studied the permeability of the meninges to penicillin in older children and determined the concentration in the cerebrospinal fluid one hour after intramuscular injection. They also studied the meningeal permeability to penicillin in infants with acute meningitis and in children with tuberculous meningitis.

They obtained the following results. After injection of a single dose of penicillin intramuscularly there is a greater concentration in the cerebrospinal fluid of the newborn infant under 1 day old than in the newborn infant over 5 days old. The difference is statistically significant. In infants under one year old penicillin can be found in the cerebrospinal fluid after an intramuscular injection. At different ages there were different concentrations, but these were not of statistical importance. In children with meningitis a greater meningeal permeability to penicillin injected intramuscularly was demonstrated.

FROM THE AUTHORS' SUMMARY.

MENINGITIS DUE TO HEMOPHILUS INFLUENZAE (PFEIFFER'S BACILLUS) TREATED, WITH CURE, BY THE METHODS OF HOYNE AND VALDÉS. J. CAMACHO GAMBA, Rev. cubana pediat. **11**:391 (July) 1949.

The author reports the case of a 3-year-old girl with meningitis due to Hemophilus influenzae who was treated with good results, by means of sulfadiazine and intramuscular injection of streptomycin. Intrathecal medication was not used.

NELSON, San Francisco.

LIPID DEGENERATION OF THE NERVOUS SYSTEM: REPORT OF AN ATYPICAL CASE OF AMAUROTIC FAMILIAL IDIOCY. O. AIDAR and J. LAMARTINE DE ASSIS, Arq. neuropsiquiat. **9**:276 (Sept.) 1951.

Aidar and de Assis report an atypical case of amaurotic familial idiocy in a 3-year-old white child whose parents were not Jewish. There was no evidence of a cherry-red spot in either retina. The child was admitted with a history of onset of convulsions six months previously. The convulsions came on after an injury to the foot, which was followed by inguinal adenopathy. There was no information as to whether fever was present at the onset of the illness. There was a history of remission for about three months. The patient was unable to walk or stand. Mental changes appeared; the child became dull and apathetic, stopped talking and crying, and swallowed with difficulty. Examination showed a dull child who was indifferent, did not talk or cry, and overreacted to external stimuli. It was difficult to determine whether she was blind. There were spastic paresis of all four limbs, a bilateral Babinski sign, generalized hyperreflexia, and cutaneous hyperesthesia. The Kahn and Wassermann reactions of the blood were negative. There were mild secondary anemia and lymphocytosis. The spinal fluid showed 53

lymphocytes per cubic millimeter; the total protein was 20 mg., the sugar 77 mg., and the chlorides 690 mm., per 100 cc. The Rh factor was negative. The fundi showed no changes. The child died of pneumonia eight months after onset of illness, which was characterized by remissions and exacerbations. During exacerbations there was usually a rise in temperature. Typical changes of amaurotic familial idiocy were found in the nervous system.

SAVITSKY, New York [A. M. A. Arch. Neurol. & Psychiat.].

FAMILIAL MYOCLONIA (UNVERRICHT-LUNDBORG SYNDROME). M. ROYOS MONTANES, Rev. españ. pediat. **7**:779 (Nov.-Dec.) 1951.

The case histories of two siblings, aged 10 and 13, in whom familial myoclonia developed a short time before the author saw them are presented in detail. The children were hospitalized and observed for 32 days.

This disease is inherited as a Mendelian recessive, and the lesion is in the dentate nucleus of the cerebellum. Fortunately, the condition is rare. The differential diagnosis of familial myoclonia and such convulsive disorders as epilepsy and Huntington's chorea, as well as the hereditary degenerative diseases, like Tay-Sachs disease (infantile amaurotic familial idiocy), amyotonia congenita, and the muscular dystrophies, is fully described.

Many of the degenerative diseases which develop in the first three years of life have a predilection for one sex. This distinguishes them from familial myoclonia, the case described being that of a brother and sister whose histories were similar not only in onset and symptoms but also in laboratory and clinical findings and progressive deterioration. The clonic contractions were persistent even in sleep, and on fluoroscopic examination small, but constant, tremors of the diaphragm were also observed.

The end-results are a rigidity typical of extrapyramidal lesions and cachexia, with death from intercurrent infection. Treatment is symptomatic and highly unsatisfactory.

ALLEN, San Francisco.

PENICILLIN THERAPY IN A CASE OF BRAIN ABSCESS IN AN INFANT. H. ZEISEL, Kinderärztl. Praxis **18**:233 (May-June) 1950.

The author found a brain abscess in a 5-month-old infant with fever, leucocytosis, and convulsions. The position was determined by air encephalography, and the abscess was punctured through the fontanel. The culture of pus removed from the abscess yielded Staphylococcus. Penicillin was injected into the abscess cavity intramuscularly. The child recovered, and repeated air encephalograms showed a return of the ventricles to a symmetrical position.

GLASER, Jerusalem.

CONVULSIONS IN EARLY CHILDHOOD AND THEIR PROGNOSIS: INVESTIGATION WITH FOLLOW-UP EXAMINATIONS OF PATIENTS TREATED FOR CONVULSIONS AT THE CHILDREN'S CLINIC OF HELSINKI UNIVERSITY. E. EKHOLM, and K. NIEMINEVA, Acta pædiat. **39**:481 (No. 6) 1950.

The authors investigated the convulsions appearing in spasmophilia and infectious disease, considering especially their prognostic significance, as revealed by follow-up examinations. The material comprised 221 children treated for convulsions in the Helsinki Children's Clinic from 1920 to 1941. The cases were classified into four groups: convulsions due to infection, 91; convulsions associated with spasmophilia, 61; miscellaneous convulsions, 54, and uncertain cases of epileptic convulsions, 15.

In the follow-up examinations special attention was paid to the patient's mental development, his adaptability to society, and the continuance of the convulsions. The percentage of patients examined was 80.9, and the period of observation was 7 to 29 years. In the investigation it was observed that in the first three groups every 10th patient, at the most, underwent mental changes.

FROM THE AUTHORS' SUMMARY.

Psychology and Psychiatry

HYPOTONIC CEREBRAL PALSY IN MENTAL DEFECTIVES. H. YANNET and F. HORTON, Pediatrics **9**:204 (Feb.) 1952.

The authors stress the relative importance of the hypotonic type of cerebral palsy in mental defectives. This condition is especially striking in cases of the severer degrees of mental defect, in which the incidence, based on the authors' institutional statistics, may approach as high as 20% of the total number of cerebral palsy cases. Clinically, it manifests itself in three forms: atonic, ataxic, and athetoid with some overlapping among these forms. The pathogenesis is variable, including genetic factors, prenatal conditions of diverse nature, birth trauma, kernicterus due to maternal isoimmunization or other mechanisms, infantile inflammatory encephalopathies, and degenerative diseases. Although few pathologic descriptions are available, it may be assumed that, on the basis of the severity of the mental defect, the high incidence of convulsive disorders, and the tendency toward microcephaly, the changes in the brain are widespread and extensive, regardless of etiology.

FROM THE AUTHORS' SUMMARY.

SIGNIFICANCE OF BRUSHFIELD'S SPOTS IN DIAGNOSIS OF MONGOLISM IN INFANCY. H. R. E. WALLIS, Arch. Dis. Childhood **26**:495 (Dec.) 1951.

The published work on mongolism has been studied with particular reference to the possibility of diagnosis in early infancy. Most authors agree that, although diagnosis is possible at birth, there is no single constant sign.

A series of infants with mongolism were observed, and it was found that all had blue eyes with white spots on the irides. These spots disappeared if the color of the iris changed to brown as the child grew older. The spots are seen in some normal children also, and their diagnostic value is not great except in a negative sense.

The first description of the spots had previously been attributed to R. L. Langdon Down, but it has been proved that the credit should go to Thomas Brushfield. It is now suggested that they should be known by his name.

KELLY, Milwaukee.

PEDIATRICS APPROACH TO PSYCHOSOMATIC MEDICINE. N. G. MOJUMDAR, Indian J. Pediat. **18**:111 (July) 1951.

The author pleads for the consideration of the child as a whole, rather than as a case of one disease or another. It is suggested that many of a child's difficulties may be traced directly to the family. Children are observant and imaginative, and the pediatrician must be constantly aware of the influence of psyche over soma in handling children.

McGUIGAN, Evanston, Ill.

GESELL'S TESTS: THEIR LIMITATIONS; THEIR PLACE IN INFANCY; CLINICAL INVESTIGATIONS. C. KOUPERNIK, Presse méd. **60**:449 (March 29) 1952.

Gesell has put forward the concept that "psychic life" starts at birth; he establishes a certain number of normal standards of development, the significance of which is unquestionable. On the other hand, he has judiciously defined the material for the tests as corresponding to the possibilities and amusement of the infant. But his concept of the development of the infant may be criticized for its not taking into account sufficiently the factors of medium and life experience. He finally admits an internal factor of organization upon which the whole development is dependent. Only this *petitio principii* enables him to consider at the same level such disparate elements as motor-postural manifestations and nascent elements of psychic life. Thus, rough findings with the tests should always be corrected by an over-all clinical impression. Further, these tests should be preceded by a precise investigation covering together the organic past and the affective climate of the family. It should be followed by a neurologic examination adapted to the infant and concerned, for instance, with the muscular tonus, postural attitudes, prehension, and facial mimicking. Such a requirement restricts the use of Gesell's tests by nonmedical psychologists.

FROM THE AUTHOR'S SUMMARY.

PSYCHOLOGICAL CONTROL OF PHRENASTHENICS TREATED WITH GLUTAMIC ACID AND PYRIDOXINE. SERGIO LEVI and M. LUISA FALORNI, Riv. clin. pediat. **48**:429 (July) 1950.

The authors, basing their findings on complete psychological controls, report on the results obtained in a group of patients affected with phrenasthenia who were submitted to six months of treatment with glutamic acid and pyridoxine. The patients sometimes showed signs of improvement in the intellectual level and sometimes showed signs of improvement in some psychic activities.

Almost constant benefits were derived from the rapidity of voluntary motor reaction to a stimulus, thus proving the importance of glutamic acid in the increase of functional activity of the nerve cells.

FROM THE AUTHORS' SUMMARY.

MOTHER AND CHILD. A. PEIPER, Kinderärztl. Praxis **18**:424 (Sept.-Oct.) 1950.

By the laws of nature the place of the human infant is with the mother, and not separated from her. Contrary to the teaching that crying children should not be picked up and carried around, the author states that the mother should follow her natural instincts and take the infant in her arms when he announces by crying that he desires the mother's love. A cradle and a pacifier can simulate the motions of the mother's body and her breast and give the child the assurance that his mother is present.

GLASER, Jerusalem.

Diseases of Genitourinary Tract

SEXUAL PRECOCITY IN FEMALES: REPORT OF TWO CASES, WITH ARREST OF PRECOCITY IN THE McCUNE-ALBRIGHT SYNDROME AFTER REMOVAL OF A CYSTIC OVARY. L. G. PRAY, Pediatrics **8**:684 (Nov.) 1951.

The author reports two cases of sexual precocity in female children. One case is that of a child with the McCune-Albright syndrome, consisting of unilateral polyostotic fibrous dysplasia, café-au-lait spots in the skin, and sexual precocity. The onset of her menses was at 3 years of age. Surgical removal, at the age of 5½ years, of an ovary containing luteinized follicular cysts and primordial follicles resulted in arrest of her sexual precocity, although not of her precocious body growth and osseous maturation. The other case is that of a child with the constitutional type of sexual precocity, by far the commonest form. In her case menstrual bleeding began at 4 years of age. Body size was large for the age, and bone age was advanced. Bioassays of the urine for gonadotropins, estrogens, and 17-ketosteroids revealed adolescent levels. Surgical exploration was carried out; no abnormalities were found except for adolescent changes in the uterus, tubes, and ovaries. The prognosis in this case appears good for a normal life and reproductive span; the only residual effect of the precocity will be moderate stunting of growth. The prognosis in the case of the child with the McCune-Albright syndrome is probably also favorable, as the fibrous dysplasia of bone does not seem progressive at this time; there will be some eventual stunting of growth in her case.

FROM THE AUTHOR'S SUMMARY.

Diseases of Ductless Glands; Endocrinology

HYPOTHYROIDISM FOLLOWING THYROIDECTOMY FOR CONGENITAL OBSTRUCTIVE GOITER. N. SCHIFRIN, and E. S. HURWITT, J. Pediat. **39**:597 (Nov.) 1951.

In the case reported the child was born with an obstructive goiter, which was removed surgically. Symptoms of hypothyroid function followed operation, and these were rectified by replacement therapy. The most significant laboratory finding in the hypothyroid state was depression of the plasma iodine.

MACDONALD, Pittsburgh.

CALCIFICATION OF THE ADRENAL GLAND IN INFANTS AND CHILDREN. F. J. RACK, and R. M. EIBEN, J. Pediat. **39**:618 (Nov.) 1951.

The authors report a case of calcification of the right adrenal gland in a 22-month-old infant, probably secondary to trauma six months before.

MACDONALD, Pittsburgh.

THE "BURNING-FEET" SYNDROME AS A COMPLICATION OF JUVENILE DIABETES. G. A. VON HARNACK, Ann. pædiat. **177**:224 (Oct.) 1951.

A case of the "burning-feet" syndrome in a juvenile diabetic is reported. The syndrome was at first described as being due to nutritional deficiency and later as being the sequel to an endogenic intoxication. In the present case both factors seem to have been contributory. Combined treatment with a mixture of dihydroergocornine, dihydroergocryptine, and dihydroergocristine ("hydergine") and vitamin V complex was successful.

FROM THE AUTHOR'S SUMMARY.

FUNCTIONAL TEST OF THE ADRENAL CORTEX IN EARLY CHILDHOOD. E. ROMINGER, Schweiz. med. Wchnschr. **82**:411 (April 12) 1952.

In healthy infants 4 to 5 months old the response of a lymphopenia to an injection of corticotropin is more definite and certain than that of an eosinopenia. Studies on sick children gave the same result but will be reported elsewhere. It is emphasized that a single test does not permit a certain conclusion as to the functional integrity of the adrenal cortex. In suspected cases other tests must be carried out.

AMBERG, Rochester, Minn.

REGRESSION OF ENDEMIC GOITER IN THE CANTON BERN, PARTICULARLY STRUMA CONGENITA. R. VON WALTHARD, Schweiz. med. Wchnschr. **82**:430 (April 12) 1952.

After 15 years of prophylaxis by means of addition of iodine to salt, the larger forms of congenital goiter are not seen anymore, but congenital goiter has not disappeared entirely. The incidence of endemic goiter in the Bern canton has diminished considerably.

AMBERG, Rochester, Minn.

EXPERIMENTAL EXOPHTHALMOS BROUGHT ON BY THIOURACIL AND THYROTROPIC HORMONE. R. PACHIOLI and G. CANDINI, Clin. pediat. **32**:439 (Aug.) 1950.

Two groups of guinea pigs were used in this study. To the first group methylthiouracil was administered. To the second group methylthiouracil and thyrotropic hormone ("ambinon") were given. Exophthalmos in marked degree appeared in the animals of the second group and persisted for three months after the treatment had been discontinued. It is worthy of note that thyrotropic hormone caused exophthalmos in animals, which were protected from thyrotoxicosis by the thiouracil medication (medical thyroidectomy!).

HIGGINS, Boston.

GOITER IN CHILDHOOD AND ITS PREVENTION: EXAMINATION OF 45,818 SCHOOL CHILDREN IN SIX DIFFERENT DISTRICTS OF SOUTHERN BAVARIA. J. BAUER, Med. Klin. **46**:530 (April 18) 1952.

In the area of southern Bavaria 45,818 school children were examined, and those with visible thyroid enlargement were noted. In some districts more than 80% of girls were afflicted. Use of table salt enriched with iodine is regarded as the most important prophylactic measure. It should be given to pregnant women to avoid congenital goiter. The addition of iodine to salt should be made obligatory by law.

AMBERG, Rochester, Minn.

EXPERIENCES WITH EPINEPHRINE TEST OF ADRENAL FUNCTIONS. B. OLDENZIEL, Nederl. tijdschr. geneesk. **95**:2257 (Aug. 4) 1951.

The author gives his experience with the epinephrine test of function of the adrenal glands. The decrease in eosinophiles was found to be the most constant sign. Probably there is a great difference in individual sensitivity to stress (pricking of the finger, as required in the test, may in itself cause a decrease in eosinophiles of 50%) and in the functional reserve for reaction to stress.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY. S. J. BRUNY and A. L. FRANKEL, Ann. Int. Med. **35**:1149, 1951.

Bruny and Frankel report pseudohypertrophic muscular dystrophy in a boy of 10 years who presented the salient features of the disease. The disease was traced back six generations in the patient's family and was found to involve males in four of the six generations.

ALPERS, Philadelphia [A. M. A. Arch. Neurol. & Psychiat.].

IMPORTANCE OF KNOWING THE BONE AGE IN EVALUATING GROWTH. G. COTELLESSA and E. DE TONI, Minerva pediat. **3**:531 (Oct.) 1951.

It is important to know the bone age of a child because of its relation to the height, weight, dentition, and sexual development.

HIGGINS, Boston.

TREATMENT OF ERB'S PARALYSIS (PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY) WITH RESECTION OF CAROTID SINUS NERVES. HUGO MEURER, Deutsche med. Wchnschr. **75**:753 (June 2) 1950.

At the time of correction of the proof of this article, the number of patients with progressive muscular dystrophy who had had a resection of the carotid-sinus nerves had increased from 17 to 250. Of the first 17, 9 were males and 8 females. Five of the 17 patients were children. The author assumes that disturbances of the regulatory function of the diencephalon can be shown in patients with this disease and suggests the possibility of a hyperfunction of the chemohumoral part of the carotid sinus. The resection of the carotid-sinus nerves was not followed by injury to the circulation or to blood pressure regulation. Clinical and subjective improvement were noted, although it is recognized that not enough time has elapsed for a final evaluation.

AMBERG, Rochester, Minn.

Cutaneous Diseases; Allergy

NUMMULAR ECZEMA IN CHILDREN. H. H. PERLMAN, J. GROPEN, and P. WESTFALL, J. Pediat. **39**:565 (Nov.) 1951.

Nummular eczema is characterized by sharply defined discoid lesions, or plaques, consisting of pinpoint vesicles, which may resemble those of atopic dermatitis or neurodermatitis, or even dermatitis herpetiformis. The authors suspect that the disease is common among children. The local treatment of choice is juniper tar N. F.

MACDONALD, Pittsburgh.

URTICARIA PIGMENTOSA. A. LIPSCHUTZ, and B. SHAFFER, J. Pediat. **39**:745 (Dec.) 1951.

A case of urticaria pigmentosa in a newborn infant is reported. The eruption involved most of the skin except for the palms and soles. Most of the lesions were nodular; a few were macular. At some sites frank wheals were seen. Many bullous lesions were observed. The pathognomonic clinical sign is urtication of the macular and nodular lesions on stroking. The characteristic pathological finding is increase in numbers of mast cells in the corium.

MACDONALD, Pittsburgh.

News and Comment

GENERAL NEWS

University of Minnesota Inpatient Psychiatric Service.—In October, an inpatient psychiatric service for children was opened at the University of Minnesota Medical School and Hospitals. This new unit will materially strengthen the over-all child psychiatry program of teaching, research, and service which has been in operation since 1938. Expansion of the program was made possible by a legislative appropriation which also provided for increased staff and stipends for training in child psychiatry. A position as instructor is available for a qualified physician desiring an academic career. Those interested should contact Reynold A. Jensen, M.D., University of Minnesota Hospitals, Minneapolis.

PERSONAL

Appointment for Dr. James G. Hughes.—Dr. James G. Hughes, associate professor of pediatrics at the University of Tennessee College of Medicine, has been advanced to the rank of professor.

Appointment for Dr. D. P. R. Keizer.—Dr. D. P. R. Keizer, Hilversum, Netherlands, has been made professor of pediatrics at the Royal College of Medicine, Bagdad, Iraq.

ANNOUNCEMENTS

Postgraduate Course in Cerebral Palsy.—The Columbia University College of Physicians and Surgeons is giving a postgraduate course in cerebral palsy from Feb. 2 to April 24, 1953. Applications should be addressed to Marguerite Abbott, Executive Director, The Coordinating Council for Cerebral Palsy, 270 Park Avenue, New York.

DEATHS

Death of Prof. Giambattista Allaria.—Giambattista Allaria, professor emeritus of clinical pediatrics of the University of Turin, died April 15, 1952, at the age of 90 years. Until 1912 pediatrics at Turin was a subdivision of the department of clinical medicine. In that year the chair of clinical pediatrics was established and Allaria became the first professor. He was the founder of the journal *La pediatria del medico practico* and in 1931 was president of the Società Italiana di pediatria. He is the author of a popular book for parents "Il libro della mamma."

Books

Developmental Disorders of Mentation and Cerebral Palsies. By Clemens E. Benda. Price, $12.75. Pp. 565, with 102 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

The book is a compendium of clinical and pathological material, collected largely in state schools for the mentally defective. The selection of cases primarily of feebleminded patients undoubtedly influences the material reported, and this is probably especially true of the section on cerebral palsy, in which the disease seems to this reviewer to be too rigidly divided into different clinical types in accordance with popular medical practice at the present time. Clinical histories and pathologic findings of 37 examples of cerebral palsy are presented and divided into three pathological types: diffuse cystic degeneration of the white matter of uncertain etiology, mantle sclerosis presumably due to arterial lesion, and a large group which is conceived of as being the result of stasis in the vein of Galen with a combination of cortical injury and status marmoratus. This collection of cases is an important contribution to the pathology of cerebral palsy but needs amplification by pathological studies on less severely damaged children from other sources in order to extend medical knowledge of the pathology of this disease.

The remainder of the pathological material presented is in large measure a compendium of material already present in the literature presented in systematized form. The concept that gargoylism may be diagnosed prior to the infiltration of bones, liver, or other structures by the abnormal metabolite is a new one to the reviewer and seems reasonable. Since mongolism is discussed by the author in a separate publication, it is not here included.

The selection of purely clinical conditions is too compressed to be useful or to be critically appraised. There is, for instance, much too much difference of opinion as to what constitutes childhood schizophrenia to allow treatment of the subject in 11 pages of which about one-half are given over to reports of two cases.

On the other hand, the discussion of the social and psychological problems of the mentally deficient is a very excellent one and the message needs wide distribution. The mentally retarded form a group so large that segregation in institutions is possible for only a small proportion and the remainder must be integrated into society as nearly as possible. Measures aimed at preserving their self-respect, initiative, and emotional security are discussed, and the importance of the early development of loyalty and affection as a basis for personality development are stressed. The emotionally oppressive effects of attempts to impose academic accomplishment on those suited mainly for concrete manipulation is discussed. The socially unsatisfactory result of the frustrations usually imposed on inadequate children is pointed out and compared to the relative socioeconomic success frequently achieved by such children when reared in stable households and freed from educational pressures. The solution of these problems depends on public understanding, the provision of suitable educational and psychiatrical resources in the school systems, and the "organization of a sufficient body of qualified persons" to administer and survey the resources of the community.

Child Rorschach Responses: Developmental Trends from Two to Ten Years. By Louise Bates Ames, Ph.D.; Janet Learned, M.A.; Ruth W. Metraux, M.A., and Richard N. Walker, M.A. Price, $7.50. Pp. 294, with bibliography and 39 tables. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1952.

The authors of this book, members of the staff of the Gesell Institute of Child Development at Yale University, gave the Rorschach test to 650 children in the age group from 2 to 10 years. Fifty children, divided equally as to sex, were studied at each age level. The discrete age levels totaled 13: half-yearly intervals from 2 through 5½ years and yearly intervals from 6 through 10 years. The children were homogeneous in above-average intelligence and socioeconomic background.

The main data of the book are the quantitative Rorschach results for each age level studied along with their interpreted developmental implications. Comparison is made between these

findings and the characteristics for each age level as advanced by Dr. Gesell. The respective findings show close correspondence. Two sample records for each age level are given in their entirety and are individually analyzed. In addition, the volume contains a thorough, rather integrative review of the existing literature on Rorschach testing of children. There is appended a full bibliography.

This volume constitutes the first report of systematic, normative Rorschach data on a fairly large, selected population of children. As such it provides opportunities to test the validity of this instrument with child subjects, and to assess the extent to which developmental and/or individual characteristics can be revealed by the test. To summarize briefly: The authors find that the test is valid for use with children, that it provides differentiated information relating to both age and individual characteristics, and that Rorschach tests of children need to be scored and evaluated within children's norms, and not those of adults.

There is no question that the data presented in this book will be immeasurably useful to workers with the Rorschach test, both in the immediate work of evaluating protocols on cases involving children and in the further investigation of theoretical questions about the test and about the development of children. For others who deal with children the main interest of the book will probably lie in the descriptions of growth and change in the psychological apparatus of the child, although much of the evidence is presented necessarily in Rorschach terms. In this connection the first few chapters of the book, which contain a discussion of Rorschach scoring variables and their rationale, may prove instructive and provocative.

Survey of Clinical Pediatrics. By Lawrence B. Slobody, M. D. Price $7.50. Pp. 471. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1952.

Dr. Slobody has designed this book as a help to enable the student and practitioner to focus on the highlights and relationships of pediatrics. In this sense it does not pretend to be a textbook.

The text, which is divided into 23 chapters, is, however, remarkably comprehensive. The chapters are written largely in a semioutline form, making for clarity and brevity. At the end of each section are questions designed to help the student focalize the information.

The book is generally excellent. For the student it forms a good basic outline; for the practitioner it will serve as a quick source of reference. Preparation for special examinations may be facilitated by its use. Collateral reading is suggested at the end of the book, consisting of the major textbooks in the field. An additional reference list is appended consisting of books on the various special subjects discussed.

This book is not too brief to be useful. It should be far more valuable than the usual "synopsis" book. At present it is the most thoroughly up-to-date book available. The book should be widely used and will undoubtedly be popular. It is recommended for students and for all those requiring refreshing or reorientation in pediatrics.

Growth of Children. By Alexander Low, M.A., M.D., LL.D. Price, 10 shillings. Pp. 64. University of Aberdeen, Aberdeen, Scotland, 1952.

This is simply a minute tabulation of all the statistics for children from 3 days to 5 years of age. Data on 66 boys and 60 girls are included in the calculations. The tables should prove to be very illuminating as references for information on the growth of children.

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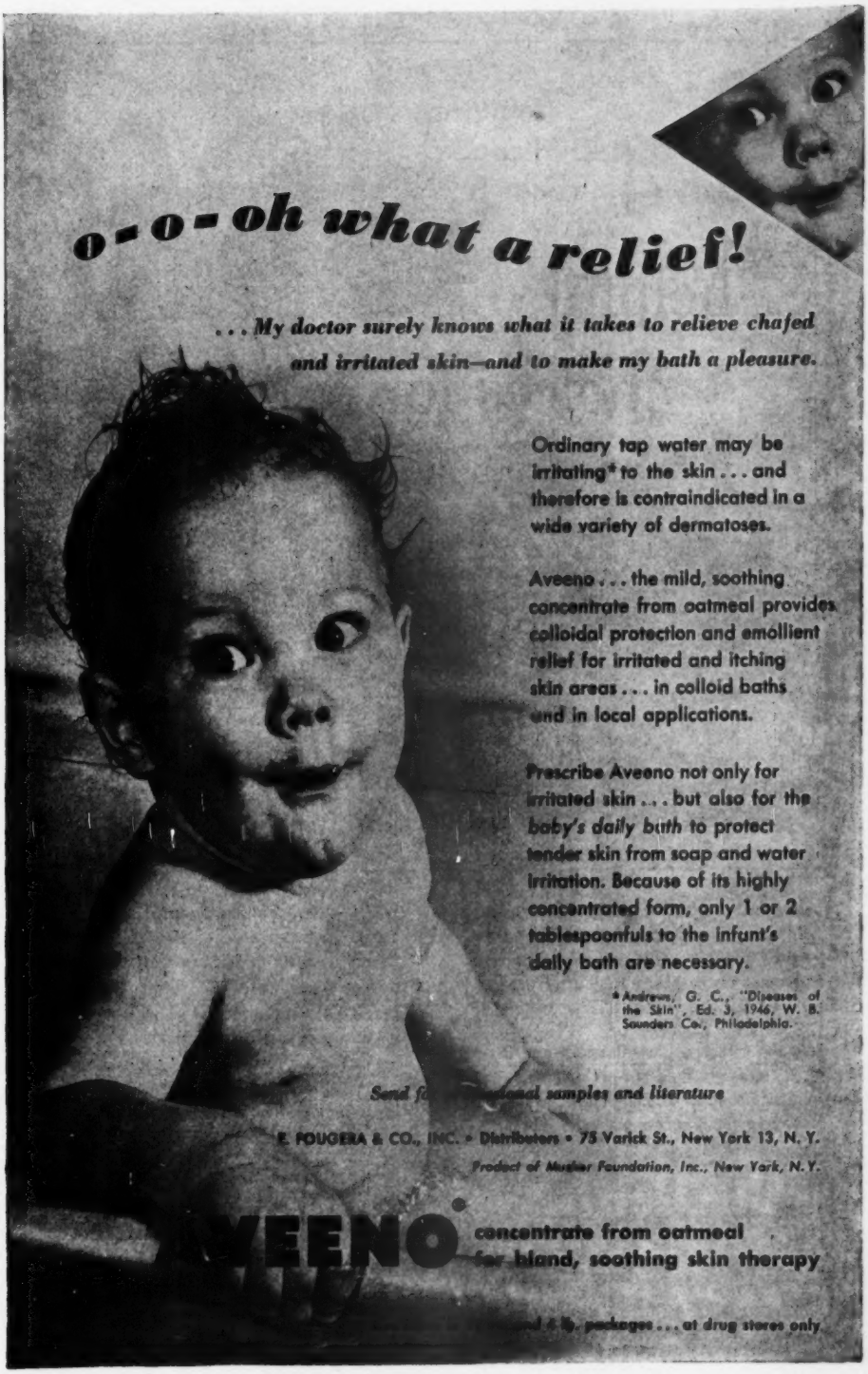
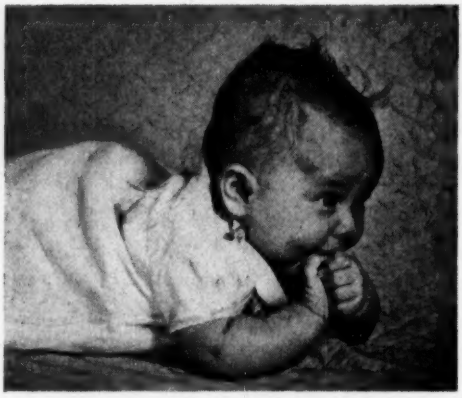
THE BAYER COMPANY DIVISION *of Sterling Drug Inc.* 1450 Broadway, New York 18, N. Y.


o-o-oh what a relief!
. . . My doctor surely knows what it takes to relieve chafed and irritated skin—and to make my bath a pleasure.
Ordinary tap water may be irritating* to the skin . . . and therefore is contraindicated in a wide variety of dermatoses.
Aveeno . . . the mild, soothing concentrate from oatmeal provides colloidal protection and emollient relief for irritated and itching skin areas . . . in colloid baths and in local applications.
Prescribe Aveeno not only for irritated skin . . . but also for the baby's daily bath to protect tender skin from soap and water irritation. Because of its highly concentrated form, only 1 or 2 tablespoonfuls to the infant's daily bath are necessary.
* Andrews, G. C., "Diseases of the Skin", Ed. 3, 1946, W. B. Saunders Co., Philadelphia.
Send for professional samples and literature
E. FOUGERA & CO., INC. • Distributors • 75 Varick St., New York 13, N. Y.
Product of Musher Foundation, Inc., New York, N. Y.
AVEENO®
concentrate from oatmeal
for bland, soothing skin therapy
packages . . . at drug stores only

4 helpful choices for baby's first "solids"



Enriched! Gerber's four starting cereals have been carefully supplemented with B-vitamins, calcium, and iron . . . the latter so exceptionally important to the young baby after pre-natal reserves fail.

One-grain! Barley, Rice, Oatmeal, and Cereal Food (wheat) are all one-grain cereals . . . to minimize chances of allergenic reactions . . . or to help you diagnose allergies.

Tempting! Gerber's Cereals are carefully made for infant-acceptance . . . with mild individual flavors . . . purée-like texture when mixed with milk or other liquids.

Convenient! Helpful to busy young mothers . . . in time and money. Thoroughly pre-cooked . . . ready to serve. Unsurpassed at any price.

FREE! Gerber's up-to-date 1952 Baby Foods Analysis Folder. Just write on your letterhead to Gerber's, Dept. 2611-2, Fremont, Michigan.

Babies are our business... our only business!

Gerber's
BABY FOODS

4 CEREALS • 40 STRAINED AND JUNIOR FOODS • 10 MEATS

provides an easily-digested, well-tolerated fat

Varamel is an evaporated formula base which contains no butterfat. In Varamel the butterfat is replaced with animal and vegetable oils in order to reduce the incidence of gastro-intestinal disturbances traceable in infant feeding to butterfat.

The fat of Varamel contains only about one-eighth as much of the less desirable fatty acids, butyric and caproic, as does butterfat—0.5% as compared to 4%.

Also, Varamel fat contains less than half as much of the slowly digested fatty acids, palmitic and stearic, as does butterfat—15% as compared to 39%.

Thus the combination of fats used in Varamel contains a minimum of both the very high and the very low molecular weight fatty acids. The combination also provides adequate amounts of the *essential* fatty acids.

The ample protein level of Varamel may also aid in fat digestion (1), and the extremely small fat globules (due to double homogenization) favorably influence fat absorption (2).

These are some of the reasons why the fat in Varamel is unusually well-tolerated and absorbed by the infant. Varamel is indicated wherever evaporated or whole milk formulas are ordinarily used.

Varamel is ethically promoted and ethically distributed.

(1) Barnes, R.H., Primrose, M.F., and Burr, G.O.—J. Nutrition 27, 179, (1944)

(2) Morales, S. et al—Pediatrics, 6, 644 (1950)

APPROXIMATE ANALYSIS

Protein	4.9%
†Carbohydrates	8.3
Fat	3.8
Ash	1.2
Calcium	0.19
Phosphorus	0.15
Iron	0.0016
Moisture	79.8
Calories per fl. oz.	32

†only from milk used—no added sugar.

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

Made from Grade A milk (U. S. Public Health Service Milk Code) which has been modified by replacement of the milk fat with animal and vegetable fats and by the addition of vitamins and iron. No carbohydrate has been added.

VARAMEL

THE BAKER LABORATORIES, INC., Cleveland 3, Ohio

Plant: **East Troy, Wisconsin.** ***Division offices:*** **Atlanta, Dallas, Denver, Greensboro, N. C., Los Angeles, San Francisco, Seattle**

MELLIN'S FOOD®

MILK MODIFIER

CONTAINS ADDED IRON AND THIAMINE

MELLIN'S FOOD®
MILK MODIFIER
CONTAINS ADDED IRON AND THIAMINE
Prepared Specially for use in Infants' Formulas
Recommended also for invalids and adults

Prepared Specially For Use in Infant's Formulas

Mellin's Food is a dried extract produced from an infusion of wheat flour, malted barley and wheat bran, admixed with potassium bicarbonate and with added thiamine and ferrous gluconate. It contains:

Available Carbohydrates	79.6%	Fat	0.2%
Maltose	58.9%	Crude Fibre	0.2%
Dextrins (by difference)	20.7%	Ash	5.9%
Protein—N x 6.25	10.3%	Thiamine	1 mgm. per 100 grams
Moisture	5.6%	Iron	17.5 mgm. per 100 grams

Calories 4 per gram, 115 per ounce, 25 per level tablespoonful.

6 level tablespoonfuls supply 1.5 times the minimum daily requirement for an infant of thiamine, and 6 mgm. of iron. RECOMMENDED ALSO FOR INVALIDS AND ADULTS.

ACCEPTED Council on Foods and Nutrition American Medical Association

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MELLIN'S FOOD COMPANY of NORTH AMERICA

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Infant Feeding Problem:

Poor appetite . . . slow rate of gain

A 4-month infant, weighing 10 lbs., 8 ozs., appeared well nourished for his build. Birth weight was 6 lbs., 2 ozs. This baby left an ounce or two at each feeding of the following formula: whole milk, 16 ozs.; water, 16 ozs.; lactose, 2 tbsp. (4½ ozs. q3h x 7 feedings).

Recommendation The baby was put on the following undiluted acid-milk mixture:

Milk	24 ozs.	} 3½ ozs. q3h x 7 feedings
U. S. P. Lactic Acid	1 dram	
Karo Syrup	2 tbsp.	

This infant's limited digestive capacity had inhibited his required intake of 55 calories per pound per day. The first approach was to offer a more digestible yet concentrated lactic acid mixture. Volume was gradually decreased, and feeding interval extended to 4 hours. The appetite gradually returned, yielding expected gains in weight. The baby thrived on the Karo Formula.

Karo Syrup . . . an ideal milk modifier for every infant

. . . prescribed for 3 generations

1. Being a balanced mixture of dextrins, maltose and dextrose, Karo is gradually absorbed . . . easily digested . . . well tolerated . . . hypoallergenic. It precludes fermentation and irritation.
2. Karo® Syrup is sterilized . . . bacteria-free, safe for feeding prematures, newborns and infants.
3. A liquid modifier is easier to use . . . soluble in hot and cold fluids . . . most economical . . . readily available.
4. Red Label and Blue Label Karo are interchangeable in all formulas. A tablespoon of Karo Syrup yields 60 calories.

Medical Division

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for
increased safety
high degree of efficacy
excellent palatability

in triple
sulfonamide therapy

council-accepted

tri-sulfameth

Each 5 cc. (approx. one teaspoonful) of syrup or each tablet provides:

Sulfamethazine	0.165 Gm.	(2.5 gr.)
Sulfadiazine	0.165 Gm.	(2.5 gr.)
Sulfamerazine	0.165 Gm.	(2.5 gr.)
Sodium Citrate*	0.5 Gm.	(7.7 gr.)

*not contained in Tri-Sulfameth Tablets

"Trials of sulfonamide combinations . . . have indicated that the occurrence of crystalluria can be decreased to negligible proportions." Virginia Medical Monthly 75:56, 1949.

PROFESSIONAL SAMPLES ON REQUEST

cf **casimir funk laboratories, inc.**
affiliate of U. S. Vitamin Corporation
250 East 43rd St., New York 17, N. Y.

Doctor:

Do the parents of your patients realize that...

- 65% of the boys and 80% of the girls of school age show foot defects?
- nearly all of these foot defects can be traced to faulty foot wear?
- the most dangerous time in the development of a child's feet is when he first begins to walk?
- it takes 10 years before the general structure of the foot is completed?

These, and many other facts, are clearly outlined for their benefit in our new booklet "Proper Care of Your Child's Feet." With almost 50 years of experience in building and designing children's shoes, Fleet-Air shoemakers are well aware of the construction features that will insure foot health and foot comfort. These booklets are prepared with a sincere effort to prevent foot faults. To secure your copies (sorry, we must limit it to 10) . . . send this coupon today.

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Rhinebeck, New York

"Special School"

Twenty-five years ago I founded a special school known as The Spruces for the treatment, adjustment and training of so-called nervous and problem children. This school was an outgrowth of my experience in starting the Child Guidance Clinic Movement under the National Committee of Mental Hygiene, and the Commonwealth Fund. At that time an urgent need was felt for a school that provided understanding guidance, adjustment and training of youngsters who could not fit into the home and school environment, but needed a special school. This school, over the years, has become a well organized unit. Some seven years ago, I purchased from Vincent Astor the Foxhollow estate, former home of his brother, John Jacob Astor Jr., and moved our Spruces children to that place, changing the name of the school to The Foxhollow School. We now have a very fine environment on an estate of some six hundred acres, providing for all the needs of youngsters of this type.

THE ANDERSON SCHOOL

Staatsburg, New York

Regents accredited college preparatory Senior and Junior High School, Elementary School, and two-year post graduate course

The Anderson School had an entirely different origin, coming from psychiatric work in industry; not clinical work, but a study of personnel problems. More particularly, The Anderson School was an outgrowth of my work in selecting, placing, and guiding in the training of college graduates who were taken on in executive training for executive jobs. Here I was struck with the tremendous lot of failures amongst so-called educated young people. My work here showed the need for a broader concept of education, emphasis on educating the emotional life and the socialization of the individual, as well as his academic training; in short, personality education. This is just what The Anderson School does. The Anderson School is a good "prep" school, fully accredited by the Board of Regents; but it emphasizes a much wider concept of student training than is conceived of in present-day education—educating the student as a person.

For further information address V. V. ANDERSON, M.D.

THE ANDERSON SCHOOL

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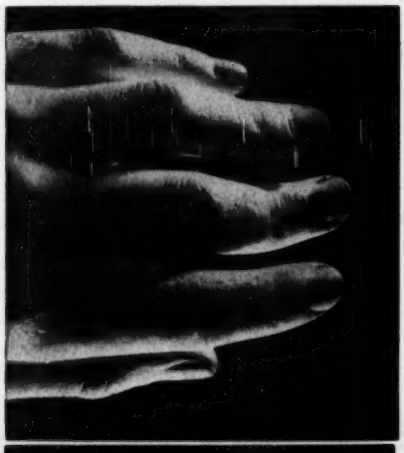

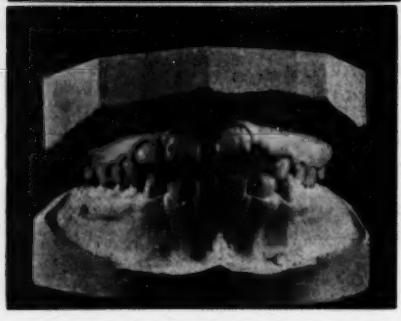

Untoward Results

OF PERSISTENT FINGER-SUCKING

MODEL

is 7½ years old. Unretouched photographs and description from a leading children's dental clinic.

Hand—sucked two middle fingers left hand since age 4. Note deformity caused.

Mouth—case shows deformed shape of mouth and displacement of teeth due to pressure of fingers.

WHEN TREATMENT IS INDICATED . . . --prescribe THUM TRADE MARK

Contains capsicum 2.34% in a base of acetone nail polish and isopropyl alcohol

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Though "boiling water" is the extent of his culinary skill, the newest of fathers can, with Similac Liquid, readily prepare a formula closely approximating human breast milk in nutritional quality and digestibility.

AS SIMPLE AS THIS . . . One part Similac Liquid added to one part sterilized water provides the standard 20 cal./fl. oz. feeding formula.

SO SIMILAR TO HUMAN BREAST MILK: *there is no closer equivalent to the milk of healthy, well-nourished mothers in prepared liquid form than*

SIMILAC *Liquid*

Provides: fat, protein and carbohydrate closely approximating the content of mother's milk in quantity and quality; 50 mg. of ascorbic acid per reliquefied quart; vitamin B_{12} and folic acid (naturally occurring, in breast milk quantities); other vitamins in adequate amounts; zero curd tension for easy and quick digestion.

Supplied: Tins containing 13 fl. oz.
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Mead's powdered formula designed for both full term and premature infants

gives a strong start for a healthy childhood

Excellent tissue turgor and muscle development in babies fed Olac® are clearly shown by steadily increasing clinical observations. These babies tend to gain weight without becoming fat, are sturdy, and resist infections well. They are generally vigorous, with happy dispositions. They get a *strong start* for a healthy childhood.

Designed for optimum nutrition of both full term and premature infants, Olac supplies milk protein in exceptionally generous amounts, to promote *sturdy growth*. Its fat is an easily digested, highly refined vegetable oil. Dextri-Maltose® supplements the lactose of the milk, to meet energy needs and spare protein for its essential tissue-building functions.

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The pleasant orange flavor, and smooth, creamy texture of St. Joseph Aspirin For Children tablets make them exceedingly palatable. That is why these tablets are so easily administered to infants and children whenever salicylic therapy is indicated. Each St. Joseph Aspirin For Children tablet contains 1¼ grains of pure, highest quality aspirin.

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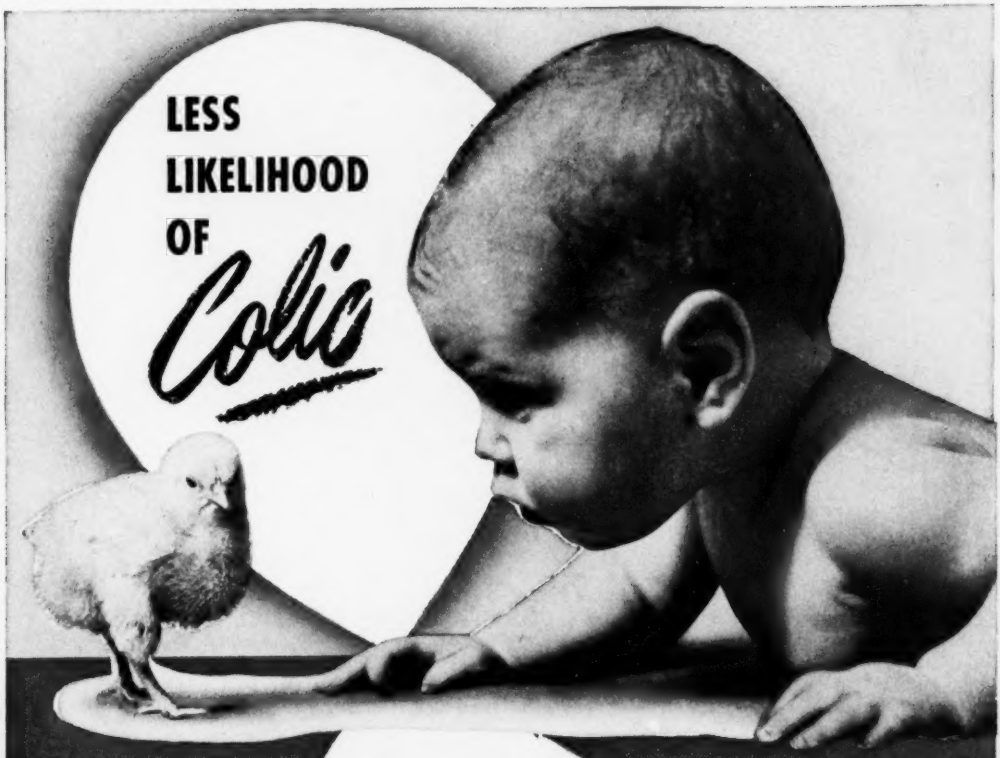

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Milk Diffusible Vitamin D_2

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- ✓ *TASTELESS*
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